CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212028Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212028
Priority or Standard	Standard
Submit Date(s)	12/27/2018
Received Date(s)	12/27/2018
PDUFA Goal Date	12/27/2019
Division/Office	DP/ODE-I
Review Completion Date	12/20/2019
Established/Proper Name	Lemborexant
(Proposed) Trade Name	DAYVIGO
Pharmacologic Class	Orexin receptor antagonist
Chemical Name	(1R,2S)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide
Applicant	Eisai Inc.
Dosage Form	Tablet
Applicant proposed Dosing Regimen	5 to 10 mg by mouth nightly before bedtime
Applicant Proposed Indication(s)/Population(s)	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4) Population: Adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	193462001 | Insomnia (disorder) |
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	193462001 | Insomnia (disorder) |
Recommended Dosing Regimen	5 to 10 mg by mouth nightly before bedtime

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Keith Kiedrow, PharmD
Nonclinical Reviewer	Amy Avila, PhD
Nonclinical Supervisor	Aisar Atrakchi, PhD
Associate Director for Pharmacology/Toxicology	Paul Brown, PhD
Office of Clinical Pharmacology	**Division** – Xiaolei Pan / TL Luning (Ada) Zhuang **Pharmacometrics** – Vishnu Sharma, Atul Bhattaram, Yuching Yang, Xinyuan (Susie) Zhang **Genomics** – Jeffrey Kraft, Christian Grimstein
Clinical Reviewer	Michelle Horner, DO
Clinical Team Leader	Mike Davis, MD, PhD
Statistical Reviewer	Jinglin Zhong, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Mike Davis, MD, PhD
Division Director (OCP)	Mehul Mehta, PhD
Division Director (OB)	Hsien Ming James Hung, PhD
Acting Division Director (DP)	Tiffany R Farchione, MD
Office Director (or designated signatory authority)	Ellis Unger, MD

Additional Reviewers of Application

OPQ	**ATL** – Wendy Wilson, PhD **Drug Substance** – Gaeton Ladouceur, PhD **Drug Product** – Dan Berger, PhD **Process and Facilities** – Chunsheng Cai, PhD **Biopharm** – Qi Zhang, Ta-Chen Wu, PhD **RBPM** – Teshara Bouie
OPDP	Christine Bradshaw; Domenic D'Alessandro
OSI	Roy Blay, PhD; Phillip Kronstein, MD
OSE	**OSE** PM – Phuong Nguyen **DMEPA** – Loretta Holmes / TL Teresa Mcmillan **DEPI** – Catherine Callahan / TL Kira Leishear **DRISK** – Leah Hart / TL Selena Ready **Drug Use** – TL Travis Ready **DPV** – Kelly Harbourt / TL Vicky Chan / MO Robert Levin
QT-IRT	Team review; DCRP contact Devi Kozeli
DBVI	Zhuang Miao
DPMH	Matthew Bacho, Carrie Ceresa (MO)
DMPP	Maria Nguyen / TL Barbara Fuller
CSS	Katherine Bonson

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION		SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Amy Avila, PhD	ON/DPT-N		Sections: 5	**Select one:** _X__ Authored ___ Approved
	Signature: see appended electronic signature				
Nonclinical SupervisorNonclinical Supervisor	Aisar Atrakchi, PhD Aisar Atrakchi, PhD	ON/DPT-N ON/DPT-N	Sections: 5	**Select one:** ___ Authored _X__ Approved	
	Signature: see appended electronic signature				
Associate Director Pharmacology/Toxicology	Paul Brown, PhD	OND/IO		Sections:	**Select one:** ___ Authored __X_ Approved
	Signature: see appended electronic signature				
Clinical Pharmacology Reviewer	Xiaolei Pan, PhD	OCP/DNP		Sections: 6 and 14.4.4	**Select one:** _ X _ Authored ___ Approved
	Signature: see appended electronic signature				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Luning (Ada) Zhuang, PhD	OCP/DNP	Section: 6 and 14.4	**Select one:** ___ Authored _ X _ Approved
	Signature: see appended electronic signature			
Pharmacometrics Reviewer	Vishnu Sharma, PhD	OCP/DPM	Section: 6, 14.4.1 and 14.4.3	**Select one:** _x__ Authored ___ Approved
	Signature: see appended electronic signature			
Pharmacometrics Team Leader	Atul Bhattaram, PhD	OCP/DPM	Section: 6, 14.4.1 and 14.4.3	**Select one:** _x__ Authored _x__ Approved
	Signature: see appended electronic signature			
PBPK Reviewer	Yuching Yang, PhD	OCP/DPM	Section: 14.4.2	**Select one:** _X__ Authored ___ Approved
	Signature: see appended electronic signature			
PBPK Team Leader	Xinyuan (Susie) Zhang, PhD	OCP/DPM	Sections: 14.4.2	**Select one:** ___ Authored _X__ Approved
	Signature: see appended electronic signature			
Clinical Pharmacology Division Director	Mehul Mehta, PhD	OCP/DNP	Sections: 6 and 14.4	**Select one:** ___ Authored _X__ Approved
	Signature: see appended electronic signature			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Michelle Horner, DO	ON/DP	Sections: 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14.2	**Select one:** __ Authored X Approved
	Signature: see appended electronic signature			
Clinical Team Leader	Mike Davis, MD, PhD	ON/DP	Sections: 1 (Authored); 2, 3, 4, 7, 8, 9, 10, 11, 12, 13 (Approved)	**Select one:** _X__ Authored _X__ Approved
	Signature: see appended electronic signature			
Division Director (Clinical)	Tiffany R Farchione, MD	ON/DP	Sections: 1-14	**Select one:** ___ Authored _X_ Approved
	Signature: see appended electronic signature			
Office Director (Clinical)	Ellis Unger, MD	Office of Drug Evaluation-I	Sections: 1-14	**Select one:** ___ Authored _X_ Approved
	Signature: see appended electronic signature			
Statistical Reviewer	Jinglin Zhong, PhD	OTS/OB/DB1	Sections:7.1, 8.1, 8.3, 14.4.3	**Select one:** _X__ Authored ___ Approved
	Signature: see appended electronic signature			
Statistical Team Leader	Peiling Yang, PhD		Sections: 7.1, 8.1, 8.3, 14.4.3	**Select one:** ___ Authored __X_ Approved
	Signature: see appended electronic signature			
Division Director (OB)	Hsien Ming James Hung, PhD		Sections: 7.1, 8.1, 8.3, 14.4.3	**Select one:** ___ Authored _X__ Approved
	Signature: see appended electronic signature			

Glossary

AE	adverse event
AUC	area under the curve
BAI	Beck Anxiety Index
BCRP	breast cancer resistance protein
BDI-II	Beck Depression Inventory – II
BMI	body mass index
CBT-I	cognitive behavioral therapy for insomnia
CCMV	complete case missing value pattern
CFB	mean change from baseline
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
CSSR	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DDI	drug–drug interaction
DSST	digit symbol substitution test
ECG	electrocardiogram
eCRF	electronic case report form
EE	ethinyl estradiol
Eh	hepatic extraction ratio
EOS	end of study
EOT	the end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GCP	good clinical practice
GD	gestation day
GI	gastro-intestinal
GLP	good laboratory practice
IR	immediate release
ISI	Insomnia Severity Index
ISS	Integrated Summary of Safety
ISWRD	irregular sleep-wake rhythm disorder
ITZ	Itraconazole
IxRS	interactive voice and web response system
KSS	Karolinska Sleepiness Scale
LH	luteinizing hormone
LPS	latency to persistence sleep
LS	least squares

MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed effect model repeated measurement
MNAR	missing not at random
MRHD	maximum recommended human dose
M-MSLT	modified MSLT
NDA	new drug application
NE	norethindrone
NOAEL	no observable adverse effect level
OH-ITZ	hydroxy-itraconazole
OSA	obstructive sleep apnea
OTC	over the counter
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamics
PK	pharmacokinetics
PND	postnatal day
PPI	patient package insert
PSG	polysomnography
PVT	Psychomotor Vigilance Test
QD	once daily
REM	rapid eye movement
RTI	reaction time index
SAE	serious adverse event
SDLP	standard deviation of the lateral position
SE	sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment emergent adverse event
TPA	tipping point analysis
UN	unstructured covariance matrix
WT	wild-type
ZOL	zolpidem

1. Executive Summary

1.1. Product Introduction

Lemborexant (developed as E2006; proposed trade name: DAYVIGO) is a new molecular entity (NME) that has been developed by the Applicant for the treatment of insomnia under IND 111871 and is being developed as a treatment for irregular sleep-wake rhythm disorder (ISWRD) (b) (4). Lemborexant is an orexin receptor antagonist and will be the second drug of this class approved in the United States for the treatment of insomnia. In this NDA, the Applicant proposes that lemborexant be approved for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)

The Applicant has developed lemborexant in the form of 5 mg and 10 mg tablets. The proposed recommended dose is 5 mg by mouth, taken no more than once per night (b) (4) (b) (4) before going to bed, with at least 7 hours remaining before the planned time of awakening. The Applicant also proposes that if the 5 mg dose is well-tolerated but greater effect is needed, the dose can be increased to 10 mg once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of lemborexant for the treatment of insomnia was demonstrated in two multi-center randomized controlled trials (Study 303 and Study 304) conducted in adults with insomnia disorder.

The primary efficacy endpoint for Study 303 was the mean change from baseline (CFB) to end of treatment at 6 months in patient-reported (subjective) sleep onset latency (sSOL), defined as the estimated minutes from the time that the patient attempted to sleep until sleep onset. Pre-specified key secondary efficacy endpoints were the mean changes from baseline to end of treatment at 6 months for patient-reported sleep efficiency (sSE) and subjective wake after sleep onset (sWASO). sSE was defined as the subjective total sleep time per subjective time spent in bed, and sWASO was defined as the number of minutes of wake during the night after initial sleep onset until the time the subject got out of bed for the day. Lemborexant 5 mg and 10 mg demonstrated statistically significant superiority to placebo on the primary and key secondary efficacy endpoints in Study 303.

The primary efficacy endpoint for Study 304 was the mean change in latency to persistent sleep (LPS) from baseline to end of treatment (day 29/30), as measured by overnight polysomnography (PSG) monitoring. LPS was defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness. Pre-specified key secondary endpoints included the mean changes from baseline to end of treatment (day 29/30) in sleep efficiency (SE) and wake after sleep onset (WASO), as measured by overnight PSG. SE was defined as the proportion of time slept asleep per time in bed, and WASO was defined as the minutes of wake

from the onset of persistent sleep until lights on. Lemborexant 5 mg and 10 mg demonstrated statistically significant superiority to placebo on the above primary and key secondary efficacy endpoints in Study 304.

The efficacy measures have been previously accepted for use in demonstrating the effectiveness of drugs indicated for the treatment of insomnia. The studies provide complementary evidence supporting the effectiveness of lemborexant, with Study 303 providing subjective (patient-reported) data from the home setting of 6 months of treatment and Study 304 providing objective (laboratory PSG-measured) data following 30 days of treatment. Both studies assessed effects of treatment on sleep initiation as well as sleep maintenance, which are core symptoms of insomnia disorder. The Applicant has thus provided substantial evidence of effectiveness for lemborexant as a treatment for insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lemborexant is an orexin receptor antagonist that has been developed for the treatment of insomnia in adults. The drug is intended to reduce the time to sleep onset and improve the maintenance of sleep by reducing the time awake during the night. We recommend that lemborexant be approved for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Insomnia is a highly prevalent symptom in the United States population, and insomnia disorder (the diagnostic population studied in the lemborexant development program) is common and associated with impairments in daily functioning and other medical comorbidities. Insomnia is more prevalent in women and older adults. The standard of care for the treatment of insomnia disorder consists of cognitive behavioral therapy for insomnia (CBT-I) and pharmacological treatments if CBT-I alone is inadequate. There are a large number of FDA-approved and off-label drugs used for the treatment of insomnia, including an orexin receptor antagonist, a melatonin receptor agonist, sedating antidepressants, benzodiazepines, and benzodiazepine receptor agonists. Current treatments for insomnia are limited by safety risks which vary by pharmacological class. The current insomnia treatment armamentarium would benefit from additional therapies with improved effectiveness, as evidenced by improvements in daytime functioning that was impaired by insomnia, as well as from therapies with improved safety profiles compared with many classes of existing treatments, particularly with respect to vulnerable populations such as elderly individuals.

Lemborexant, at dosages of 5 mg and 10 mg nightly, was demonstrated to decrease sleep latency and improve sleep maintenance as compared with placebo. The benefits were demonstrated subjectively by patient-completed sleep diaries as well as objectively by polysomnography. The benefits were also demonstrated in the context of sub-acute (30 days) and chronic (6 months) treatment. The 10-mg dose of lemborexant did not appear to be markedly more effective than the 5-mg dose at the group level, but data suggested that the 10-mg dose may provide the optimal benefit for some patients. As the second drug of its class approved for the indication of insomnia, it is expected that lemborexant will provide a meaningful addition to the armamentarium of insomnia treatments, but there was no clear evidence that lemborexant would provide greater benefit than the currently marketed orexin receptor antagonist.

The safety database for lemborexant included 1847 subjects with any sleep disorder who were exposed to at least one dose of lemborexant during the development program. The database included 708 subjects exposed to lemborexant for ≥6 months and 434 subjects for 12 months, which was an adequate duration of exposure to facilitate pre-marketing characterization of safety. The most common adverse reactions to

lemborexant were somnolence/fatigue, headache, and nightmare/abnormal dreams. Other significant adverse reactions that occurred infrequently in phase 3 studies included sleep paralysis, hypnagogic hallucinations, and complex sleep behaviors. The safety of lemborexant in patients with moderate to severe respiratory conditions and in women who were pregnant or breastfeeding was not characterized in the development program. The safety concerns of lemborexant can be managed in the postmarket setting by labeling known and anticipated risks, postmarketing pharmacovigilance, and the conduction of postmarketing safety studies.

In conclusion, considering the balance of benefits and risks that were observed in the development program, we recommend that lemborexant be approved for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Because the 10-mg dose of lemborexant was associated with a higher incidence of adverse reactions and for many patients may not be necessary to achieve the desired benefit, the recommended dose should be 5 mg nightly, which may be increased to the maximum dose of 10 mg nightly based on clinical response and tolerability. The product label should include warnings and precautions for significant safety concerns anticipated according to the drug class as well as findings from the development program. The Applicant should conduct postmarketing studies to assess the respiratory safety of lemborexant in patients with moderate to severe respiratory conditions and the safety of lemborexant in pregnant and breastfeeding women.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Insomnia* is broadly characterized by difficulty in initiating and/or maintaining sleep. The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria for *insomnia disorder* require a predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the symptoms of difficulty initiating sleep, difficulty falling asleep, or early-morning awakening with inability to return to sleep. The sleep disturbance in insomnia disorder must also cause clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. • An estimated 30% of adults in the United States report insomnia symptoms at a given time, with 10 to 15% of the population experiencing daytime impairment and 6 to 10% meeting diagnostic criteria for insomnia disorder. • Insomnia can occur at any stage in life, but the first episode tends to occur in young adulthood. Insomnia is more prevalent in women than men (gender	Insomnia is a highly prevalent symptom in the United States population. Insomnia disorder (the condition studied in the lemborexant development program) is common and associated with impairments in multiple aspects of daily functioning as well as other medical comorbidities. Insomnia is more prevalent in women and older adults, so it is important that an adequate number of individuals in these populations be included in development programs evaluating treatments for insomnia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ratio 1.28 to 1.46:1 across age groups), and the first onset in women is frequently associated with the birth of a child or menopause. Insomnia is more prevalent in middle-age and older adults than in younger adults; nearly 50% of the elderly population report symptoms of insomnia, and 12 to 20% of the elderly population meet criteria for insomnia disorder. • The course of insomnia is variable. For many individuals, situational insomnia may last a few days or weeks before resolving once the precipitating situation has subsided. However, a substantial proportion of individuals with insomnia (45 to 75%) experience it chronically. • In addition to nighttime sleep difficulties, the daytime impairments frequently associated with insomnia include fatigue, decreased cognitive performance, mood disturbances, and disruptions in social and occupational functioning. Chronic insomnia is also associated with medical comorbidities, including diabetes, coronary heart disease, and chronic obstructive pulmonary disease; it is thought that insomnia increases the risk of medical comorbidities and medical comorbidities increase the risk of insomnia.	
Current Treatment Options	• Current practice guidelines recommend that adults receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder, and that pharmacological treatments be considered if CBT-I alone is inadequate. CBT-I includes multiple components targeting the thoughts and behaviors associated with insomnia. • It is estimated that 20% of adults in the United States use prescribed and over-the-counter medications for insomnia every month. FDA-approved medications for the treatment of insomnia include an orexin receptor antagonist, a melatonin receptor agonist, a tricyclic antidepressant, and multiple benzodiazepines and other benzodiazepine receptor agonists ("z-drugs"). Medications frequently prescribed off-label for the treatment of	In addition to the non-pharmacological treatment of CBT-I, there are a large number of FDA-approved and off-label drugs used for the treatment of insomnia disorder. Although approved pharmacological treatments have been found to improve sleep initiation and/or sleep maintenance, their use is often associated with a variety of adverse reactions. The treatment armamentarium would benefit from

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	insomnia include other sedating antidepressants such as trazodone and mirtazapine. Sedating antipsychotic medications are sometimes prescribed off-label for the treatment of insomnia, but this is not advised by practice guidelines due to their risk profile. Over-the-counter drugs and nutritional supplements used for the treatment of insomnia include antihistamines (i.e., diphenhydramine and doxylamine) and melatonin. • The safety risks of medications for the treatment of insomnia vary according to their pharmacodynamic and pharmacokinetic profiles. Benzodiazepines and other benzodiazepine receptor agonists are associated with residual daytime sedation, dizziness, lightheadedness, cognitive impairment, and motor incoordination. Many hypnotic drugs can also suppress respiration and worsen obstructive sleep apnea; the respiratory effects of benzodiazepines are increased when used in combination with opioids, alcohol, or other central nervous system depressants. Long-term use of hypnotic drugs is also associated with dependence, and withdrawal symptoms such as rebound insomnia may occur following discontinuation. Parasomnias, including complex sleep-related behaviors such as sleepwalking or sleep driving, can occur in association with hypnotic drugs, and current labeling for "z-drugs" includes a boxed warning for complex sleep-related behaviors. Common adverse reactions to melatonin receptor agonists include somnolence, dizziness, fatigue, and nausea, and common adverse reactions to the orexin receptor antagonist suvorexant include daytime somnolence, headache, and abnormal dreams. • Older adults generally have a higher risk of experiencing adverse reactions from hypnotic drugs, and reactions more prevalent in elderly populations include excessive sedation, cognitive impairment, delirium, night wandering, agitation, and balance problems/falls. Patients with respiratory conditions such as obstructive sleep apnea and chronic obstructive pulmonary disease	additional therapies with improved effectiveness, particularly as evidenced by improvements in daytime functioning that was impaired by insomnia. The armamentarium would also benefit from novel therapies with improved safety profiles compared to existing therapies, particularly with respect to vulnerable populations such as elderly individuals.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	are at an increased risk for respiratory depression with hypnotic drugs. • The effectiveness of current FDA-approved medications was generally demonstrated based on their superiority to placebo in reducing the time needed to fall asleep (sleep latency) and/or the time awake during the night after initially falling asleep (wake after sleep onset). There is less evidence on whether their benefits on sleep parameters translate to functional improvements in patients with insomnia disorder. There is also limited evidence comparing the effectiveness between different medications or classes of medications for the treatment of insomnia.	
Benefit	• The effectiveness of lemborexant was demonstrated in two adequate and well-controlled trials conducted in adults with insomnia disorder. In the placebo-controlled phase of Study 303 patients were randomized to receive lemborexant 5 mg (n=323), lemborexant 10 mg (n=323), or placebo (n=325) for 6 months. In Study 304, patients were randomized to receive lemborexant 5 mg (n=266), lemborexant 10 mg (n=269), placebo (n=208), or the active comparator zolpidem ER 6.25 mg (n=263) for 30 days. • The primary efficacy endpoint for Study 303 was the mean change from baseline (CFB) to end of treatment (6 months) in patient-reported (subjective) sleep onset latency (sSOL), defined as the estimated minutes from the time that the patient attempted to sleep until sleep onset. Pre-specified key secondary efficacy endpoints were the change from baseline to end of treatment at 6 months for patient-reported sleep efficiency (sSE) and subjective wake after sleep onset (sWASO). • The primary efficacy endpoint for Study 304 was the mean change in latency to persistent sleep (LPS) from baseline to end of treatment (day 29/30), as measured by overnight polysomnography (PSG) monitoring. LPS was defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness. Pre-specified key secondary endpoints were the mean	The Applicant has provided substantial evidence of effectiveness for lemborexant as a treatment for insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The results from the pivotal efficacy trials are complementary, assessing treatment effects on sleep initiation and maintenance with both sub-acute (30 days) and chronic (6 months) treatment. Although lemborexant 10 mg did not appear markedly more beneficial than 5 mg when comparing mean treatment effects, assessment of proportions of patients with different magnitudes of response suggests that, for some patients, the 10 mg dose may provide the optimal benefit. It is

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
change from baseline to end of treatment (day 29/30) in sleep efficiency (SE) and wake after sleep onset (WASO), as measured by overnight PSG.
• The primary and key secondary efficacy measures have been previously accepted for use in demonstrating the effectiveness for drugs indicated for the treatment of insomnia. They assess sleep parameters which measure fundamental aspects of insomnia disorder (initiation and maintenance of sleep).
• In both studies, lemborexant 5 mg and 10 mg were statistically superior to placebo on the primary and key secondary endpoints (see summary table below).

<table>
<tr><th>Endpoint</th><th>Lemborexant 5 mg Treatment Effect (95% CI)</th><th>Lemborexant 10 mg Treatment Effect (95% CI)</th></tr>
<tr><td>Study 303 sSOL[a]</td><td>0.7 (0.6, 0.8)</td><td>0.7 (0.6, 0.8)</td></tr>
<tr><td>Study 303 sSE[b]</td><td>4.6 (2.2, 6.9)</td><td>4.7 (2.4, 7.0)</td></tr>
<tr><td>Study 303 sWASO[b]</td><td>-17.5 (-27.3, -7.6)</td><td>-12.7 (-22.4, -3.0)</td></tr>
<tr><td>Study 304 LPS[c]</td><td>0.6 (0.6, 0.7)</td><td>0.6 (0.5, 0.7)</td></tr>
<tr><td>Study 304 SE[d]</td><td>3.9 (2.5, 5.3)</td><td>4.9 (3.5, 6.3)</td></tr>
<tr><td>Study 304 WASO[d]</td><td>-7.7 (-13.4, -2.1)</td><td>-9.1 (-14.8, -3.5)</td></tr>
</table>
[a]Treatment effect refers to the ratio of [Month 6 sSOL / Baseline sSOL] for lemborexant versus placebo, such that a smaller ratio corresponds to a greater improvement.
[b]Treatment effect refers to the treatment difference between lemborexant versus placebo, such that a larger value for sSE and smaller value for sWASO corresponds to a greater improvement.
[c]Treatment effect refers to the ratio of [Day 29/30 LPS / Baseline LPS] for lemborexant versus placebo, such that a smaller ratio corresponds to a greater improvement.
[d]Treatment effect refers to the treatment difference between lemborexant versus placebo, such that a larger value for SE and smaller value for WASO corresponds to a greater improvement.

•A strength of the efficacy results across the pivotal trials are that they provide complementary evidence for supporting the effectiveness of lemborexant, with
</td><td>expected that lemborexant will provide a meaningful addition to the armamentarium of drugs approved for the treatment of insomnia and will be the second drug of its class approved for this indication.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Study 303 providing subjective (patient-reported) data from the home setting for 6 months of treatment and Study 304 providing objective (laboratory polysomnography-measured) data after 30 days of treatment. •Analyses of histograms presenting the proportion of patients experiencing various magnitudes of improvement on the primary and key secondary endpoints (see Sections 8.1.2 and 8.1.4) suggest that the benefits will be clinically meaningful to patients. As one example, in Study 304 there was a dose-dependent numerical increase in the percentage of patients who experienced a decrease in sleep initiation time of 75 to <100 minutes. The clinical meaningfulness of primary and key secondary results was also supported by additional patient-reported secondary efficacy measures. •There were no clear differences in effectiveness according to subpopulations (age, sex, race), although the studies were not designed and powered to draw conclusions on differences across subpopulations.	
Risk and Risk Management	• The safety database from the phase 3 Studies 303 and 304 included 785 subjects exposed to lemborexant (5 or 10 mg) for ≥3 months, 708 subjects for ≥6 months, 456 subjects for ≥9 months, and 434 subjects for 12 months. In total, 1847 subjects with any sleep disorder were exposed to at least 1 dose of lemborexant during the development program. The extent of exposure in the safety database exceeds the minimum recommended by guidance on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. • The overall understanding of the lemborexant safety profile is informed, in part, by the pre- and post-marketing safety findings for suvorexant, which is the only orexin receptor antagonist currently approved for use. • The safety database from Studies 303 and 304 included adequate representation from patient subpopulations with the greatest expected use in the target patient population. Specifically, approximately 35% of patients	The safety profile of lemborexant is adequately characterized for the anticipated patient population. The safety profile appears to be generally similar to that of the orexin receptor antagonist currently approved for use (suvorexant). The Applicant should conduct postmarketing studies to evaluate remaining safety uncertainties, including the potential for respiratory depression in patients with moderate to severe compromise in respiratory

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exposed to lemborexant were ≥65 years of age and approximately 75% were women. • The most common adverse reaction to lemborexant was somnolence/fatigue. In the analysis pool consisting of the first 30 days of treatment in Studies 303 and 304, the incidence of somnolence/fatigue was 9.6% for lemborexant 10 mg, 6.9% for lemborexant 5 mg, and 1.3% for placebo. The incidence of somnolence in patients receiving lemborexant 10 mg was higher in patients ≥65 years of age than patients <65 years of age. In this analysis pool, other adverse reactions which occurred in ≥2% of patients receiving lemborexant and at a greater frequency than placebo were headache and nightmare/abnormal dreams. • In the 6-month placebo-controlled phase of Study 303, the incidence of discontinuation due to adverse reactions was relatively low (placebo: 3.8%, lemborexant 5 mg: 4.1%, and lemborexant 10 mg: 8.3%). The most common adverse reactions leading to discontinuation of treatment were somnolence and nightmares. • Other significant adverse reactions observed in Studies 303 and 304 were sleep paralysis (placebo: 0%, lemborexant 5 mg: 1.3%, lemborexant 10 mg: 1.6%), hypnagogic hallucinations (placebo: 0%, lemborexant 5 mg: 0.1%, lemborexant 10 mg: 0.7%), and complex sleep behaviors (n=2 patients, both receiving lemborexant 10 mg). • The concomitant use of lemborexant with CYP3A4 inhibitors increases the exposure to lemborexant and may increase the risk for adverse reactions. Therefore, lemborexant should not be used concomitantly with strong or moderate CYP3A4 inhibitors. • The Applicant conducted several special safety studies to evaluate safety concerns of special interest for insomnia treatments. Lemborexant did not appear to impair awakening in response to sound. When patients were	function and the safety of lemborexant use during pregnancy and breastfeeding. Following completion of the postmarketing studies, the new safety information should be incorporated in labeling. The known risks of lemborexant use can be managed by product labeling, and ongoing post-marketing pharmacovigilance will be important to monitor for safety signals that were not observed in the development program. The product label should include warning and precautions for significant safety concerns anticipated based on the drug class and findings from the development program. These include the potential for CNS depressant effects and daytime impairment, sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy-like symptoms, complex sleep behaviors, respiratory depression, and worsening of depression or suicidal ideation. The label should also include the results of special safety studies that were

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	awoken in the middle of the night, lemborexant was associated with dose-dependent worsening in measures of postural stability, attention, and memory. There were no meaningful differences on next-day postural stability, attention, or memory with lemborexant as compared to placebo. In a driving study, although there were no statistically significant effects of lemborexant as compared to placebo, driving ability was impaired in some subjects who received lemborexant 10 mg. Analyses on the potential for withdrawal effects following lemborexant discontinuation suggested that lemborexant does not have meaningful withdrawal effects or rebound insomnia. • The Applicant did not assess for the potential of lemborexant to cause respiratory depression in patients with moderate to severe obstructive sleep apnea or chronic obstructive pulmonary disease. Because hypnotics are frequently used in elderly patients who may have compromised respiratory function and many hypnotics are associated with respiratory depression, the lack of this information is a safety uncertainty. In addition, the safety of lemborexant use during pregnancy or breastfeeding is not well established.	conducted to evaluate safety concerns of special interest for hypnotics.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.1, 8.1.2, 8.1.3, 8.1.4
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		X	Performance outcome (PerfO)	8.1.3, 8.1.4
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Insomnia disorder is characterized by "chronic dissatisfaction with sleep quantity or quality that is associated with difficulty falling asleep, frequent nighttime awakenings with difficulty returning to sleep, and/or awakening earlier in the morning than desired" [1]. Two main classification systems are currently used to define insomnia disorder, the Diagnostic and Statistical Manual-5 (DSM-5) and the International Classification of Sleep Disorders-3 (ICSD-3). Both classification systems use similar criteria for insomnia disorder, including requiring difficulty with sleep and functional impairment. Table 1 details the DSM-5 criteria for insomnia disorder, which is commonly used in psychiatric clinical settings (DSM-5, 2014).

Table 1: DSM-5 Diagnostic Criteria for Insomnia Disorder

A	A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:	1. *Sleep-onset insomnia* (or *initial insomnia*): Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.) 2. *Sleep maintenance insomnia* (or *middle insomnia*): Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.) 3. *Late insomnia:* Early-morning awakening with inability to return to sleep.
B	The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning	
C	The sleep difficulty occurs at least 3 nights per week.	
D	The sleep difficulty is present for at least 3 months.	
E	The sleep difficulty occurs despite adequate opportunity for sleep.	
F	The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).	
G	The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).	
H	Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.	

Abbreviation: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
[a]American Psychiatric Association, 2014; published online.

The DSM-5 also provides specifiers for comorbidities (e.g., medical, other sleep disorders) and frequency (e.g., e*pisodic*: symptoms last at least 1 month but less than 3 months; *persistent*: symptoms last 3 months or longer; and, *recurrent*: two (or more) episodes within the space of one year).

Insomnia disorder is distinct from the general term *insomnia*, which refers to the inability to sleep during the period when sleep should normally occur [2]. The DSM-5 estimates that 30% of the general US population have symptoms of insomnia during the lifetime, 10 to 15% experience daytime impairment, and 6 to 10% will meet criteria for insomnia disorder [3]. Insomnia can occur at any stage of life, but the first episode tends to start in young adulthood. Insomnia symptoms increase in frequency with age, with nearly 50% of the elderly population reporting symptoms of insomnia and 12 to 20% meeting criteria for insomnia disorder, in part due to physiological changes in sleep patterns and higher incidence of health problems [4]. Impaired sleep is more prevalent among females than males, ranging from 1.28:1 to 1.46:1 ratio of females to males [5]. Recurrence of insomnia is common, with chronicity reported in 45 to 75% of those with insomnia disorder.

Comorbidities, both psychiatric and medical, are common with insomnia disorder. Approximately 40 to 50% of adults with insomnia present with a comorbid psychiatric diagnosis, and symptoms of depression, anxiety, and cognitive changes are common [3]. Medical comorbidities such as breathing-related sleep disorders, pain disorders, neurological conditions, and thyroid disorders can disrupt sleep and may be worsened by sleep. Chronic disruption of sleep is associated with impairments in health, including cardiac disease, hypertension, and cognitive disfunction. Insomnia disorders are associated with disruptions in interpersonal, social, occupational, and general daily functioning.

Among individuals with insomnia, sleep maintenance symptoms are most commonly reported (50% to 70%), followed by difficulty in initiating sleep (35% to 60%) and nonrestorative sleep (20% to 25%) [6]. In the clinical and research settings, the aforementioned sleep parameters can be measured subjectively (e.g., sleep diary and questionnaires), or subjectively (e.g., using overnight polysomnography (PSG) testing). For reference, the examples of commonly used sleep parameters are listed below:

> **Latency to Persistent Sleep (LPS):** LPS is measured using PSG. LPS can be described as the minutes from lights off to the consecutive period of non-wakefulness (e.g., 10 of non-wakefulness based on PSG electrophysiological data).
>
> **Sleep Efficiency (SE):** The proportion of time spent asleep per time in bed calculated as total sleep time (TST) divided by the interval from “lights off” until “lights on”; can be measured by sleep diary or PSG.
>
> **Sleep Onset Latency (SOL):** Time to fall asleep; defined as the estimated minutes from the time that the patient attempted to sleep until sleep onset. Average is ~11 to 23 minutes in adults and ~9 minutes in elderly; can be measured by sleep diary.
>
> **Total Sleep Time (TST):** Number of minutes asleep.
>
> **Wake After Sleep Onset (WASO):** Minutes of wake from the onset of persistent sleep until lights on. Can be measured by sleep diary or PSG.

Wake After Sleep Onset Second Half of the Night (WASO2H): Minutes of wake during the interval from 240 minutes after lights off until lights on; can be measured by PSG.

2.2. Analysis of Current Treatment Options

The American College of Physicians (ACP) Guidelines recommends that "all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder," and that pharmacological therapy can be considered when CBT-I alone is unsuccessful [7]. CBT-I combines cognitive therapy with behavioral interventions related to sleep (sleep hygiene, sleep restriction, environmental controls). CBT-I is widely available via therapists, internet websites, and self-help books. Systematic reviews of randomized control trials (RCTs) describe the effectiveness of several non-pharmacological therapies for insomnia disorder in RCTs, including CBT-I, behavioral therapy, stimulus control, relaxation strategies, and sleep restriction [8].

Multiple drug classes are commonly used for the treatment of insomnia disorders, including benzodiazepines, benzodiazepine receptor agonists, melatonin receptor agonists, orexin receptor antagonists, and tricyclic antidepressants, including for use in elderly populations [7].

The most frequently used insomnia medications are non-benzodiazepine hypnotics (e.g., zolpidem) and other drugs used off-label, such as, trazodone, or over-the-counter medications, such as melatonin, and anti-histamine agents. The Applicant's Clinical Overview documentation states that that zolpidem accounts for (b)(4)% of US prescriptions for insomnia, and trazodone (b)(4)% of prescriptions, according to data from Intercontinental Medical Statistics (IMS).

Table 2 provides a list of medications used to treat insomnia. The list includes FDA-approved indications for insomnia, the common over-the-counter medications, and the dietary supplement melatonin. Several drugs listed in Table 2 are rarely used in the clinical setting today because newer drugs have a more advantageous risk to benefit profile. Estazolam (Prosom), Flurazepam (Dalmane), Secobarbital (Seconal) have a history of FDA approval for insomnia but were not listed in Table 2 because they have been discontinued.

Table 2: Summary of Treatment Armamentarium Relevant to Insomnia Disorders

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
Orexin receptor antagonist				
Suvorexant (Belsomra)	Sleep onset and/or sleep maintenance 2014	Tablets, 5 mg, 10 mg, 15 mg, 20 mg	Two 3-month RCTs, studied in elderly and non-elderly adults	-DDI CYP3A inhibitors, Strong CYP3A inducers -Not recommended with severe hepatic impairment -W&P includes daytime somnolence, parasomnias, depression, respiratory function

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
Melatonin receptor agonist				
Ramelteon (Rozerem)	Sleep onset 2005	8 mg	3 PBO DB RCTs; 35 days in non-elderly adults (8, 16 mg); 3-period crossover Elderly (4 or 8 mg); 6 months efficacy and safety in adults (8 mg)	-W&P include anaphylaxis, parasomnias, depression, CNS impairment, reproductive effects, avoid with severe sleep apnea. Do not take with high fat-meal or fluvoxamine - -Elevated prolactin levels and testosterone may occur
Antidepressants				
Doxepin (Silenor)	Sleep maintenance Doxepin Approved in 1969 Silenor Approved in 2010	6 mg adults, 3 mg elderly	6 PBO DB RCTs up to 3 months duration, ages 18-83 with chronic or transient insomnia	-Contraindication with MAOIs, narrow angle glaucoma -W&P: parasomnias, complex behaviors, depression, overdose potential, a CNS-depressant, not for use with severe OSA or in pregnancy. DDI with MAOIs, cimetidine, alcohol, CNS depressants -need to reduce quantity to avoid intentional overdose -Parent drug half-life 15 hours -Not to be taken within 3 hours of a meal -Anticholinergic effects
Benzodiazepines/ gamma-aminobutyric ($GABA_A$) agonist				
Quazepam (Doral)	Difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings 1985	7.5 mg	Placebo-controlled 5-night and 28-night studies (15 mg); 7 day double-blind, Controlled study in elderly (7.5 mg)	-Long-acting BZD -W&P: CNS depressant, risk for tolerance, withdrawal, overdose, parasomnias, worsening depression or suicidal thinking, need to reduce quantity to avoid intentional overdose -Potentially fatal with opioids -Long duration of action Elimination half-life with active metabolite, 39 hours

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Triazolam (Halcion)	short-term treatment of insomnia (generally 7–10 days) 1982	0.25 mg; patients with low body weight may use 0.125. Do not exceed 0.5 mg daily	1003 patients in multiple placebo controlled studies, 1 to 42 days long	-Short-acting BZD -Contraindicated in pregnancy and-P450 3A (CYP 3A) mediated medications -W&P: Parasomnias, worsened insomnia, anaphylaxis, CNS depressant, Potentially fatal with opioids; also tolerance, withdrawal, overdose potential -Short half-life of parent drug and duration of action -Lower dose for the elderly -"Use for more than 2–3 weeks requires complete reevaluation of the patient"
Temazepam (Restoril)	Short-term insomnia treatment, 7-10 days 1981	7.5 mg, 15 mg, 30 mg. Recommend dose is 15 mg.	Placebo controlled, 2-week studies (7.5, 15, and 30 mg)	-Intermediate-acting BZD -Fetal Harm, not for use in pregnancy -W&P: DDI, withdrawal symptoms, abuse potential, anaphylaxis; daytime sedation. -Half-life of 9 hours -No dose adjustment for liver disease
Non-Benzodiazepine GABAA receptor agonists				
Eszopiclone (Lunesta)	To decrease sleep latency and improve sleep maintenance 2004	1 mg recommended initial dose; up to 3 mg	2100 subjects ages 18-86 with chronic and transient insomnia in 6 PBO-controlled trials up to 6 months, with 523 elderly patients	-Half-life ~6 hours -Boxed warning for complex sleep behaviors -W&P: CNS depressants, parasomnias, worsening depression/suicidal thinking; withdrawal; need lower dose for elderly, hepatic impairment, respiratory function, hemodynamic responses - abuse potential similar to BZD, risk of overdose -Avoid in pregnancy
Zaleplon (Sonata)	Sleep onset insomnia only 1999	5 mg, 10 mg, 20 mg	3435 patients in 12 PBO- and active-drug controlled clinical trials; 1019 elderly patients	-Half-life ~ 1 hour -Boxed warning for complex sleep behaviors -No effect on duration of sleep and number of wakenings -Safety: Memory impairment, sedation, withdrawal anxiety and insomnia -W&P: Parasomnias, complex sleep behaviors, abnormal thinking, CNS-depressant, next-day impairment, withdrawal effects, abuse potential similar to BZD -Reduce dose with moderate hepatic insufficiency and elderly/ill patients -Avoid in pregnancy

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
Zolpidem Tartrate (Ambien)	short-term treatment of insomnia characterized by difficulties with sleep initiation 1992	5 mg for women; 5 or 10 mg for men	DB, PBO single night for transient insomnia (N=462; 7.5 and 10 mg); 2 night trial in elderly adults (N=35, does 5, 10, 15, 20 mg); Chronic insomnia: 5 week DB (N=75), parallel, PBO-controlled (10 mg) and 4 week (n=141, 10 mg)	-Half-life 1.4 to 4.5 hours -Boxed warning for complex sleep behaviors -W&P: Parasomnias, complex sleep behaviors, abnormal thinking, CNS-depressant, next-day impairment, withdrawal effects, abuse potential similar to BZD -Risks of tolerance, dependence, abuse, and daytime sedation, parasomnia -Reduce dose with severe hepatic insufficiency and elderly -Formulation for sleep onset only -Avoid in pregnancy
Zolpidem CR (Ambien CR)	Sleep onset and/or sleep maintenance 2005	6.25 mg for women, elderly, and hepatic impairment; 6.25 mg or 12.5 mg for men.	Three PBO-DB RCTs: 3-week, Ages 18-63 (N=212, 12.5 mg); 3-week, age ≥65 (N=205; 6.25 mg); 24-week Ages 18-64, N=1025), PRN usage 12.5 mg	-Boxed warning for complex sleep behaviors -W&P: Parasomnias, complex sleep behaviors, abnormal thinking, CNS-depressant, next-day impairment, withdrawal effects, abuse potential similar to BZD - Risks of tolerance, dependence, abuse, and daytime sedation, parasomnia -Avoid in pregnancy
Other formulations of Zolpidem Tartrate Zolpimist: Approved 2008, oral spray 10 mg (5 mg elderly/hepatic), for sleep initiation Edluar: Approved 2009, sublingual form 5 mg or 10 mg, indication for sleep initiation); Intermezzo: Approved 2011, sublingual form 1.75 mg for women and 3.5 mg for men, indication for "treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep"				
Medications Used Off-Label in the Treatment of Insomnia				
Trazodone	Off-label; Sleep onset or sleep maintenance insomnia	50 mg 100 to 200 mg	Small effect sizes observed in a randomized trial in patients with primary insomnia	-Commonly used in adults and youth -Increased risk of suicidality, postural hypotension -AASM recommends against use due to short-term effect and limited data -Metabolized by CYP3A4 to an active metabolite; use with caution in combination with other serotonergic drugs

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
Amitriptyline	Off-label	10 mg titration up to 50 or 75 mg		Tricyclic antidepressants are used less frequently
Butabarbital (Butisol)	"Use as a sedative or hypnotic" (sleep induction and sleep maintenance) 1939	50 to100 mg	Approved in 1939	-Barbiturates lose their effect after two weeks -W&P: Parasomnias, complex behaviors, habit forming, masks pain, fetal damage -Avoid in individuals with depression, suicidal tendencies, history of drug abuse. Abuse potential. Risk of overdose (dispense small amounts) -Contraindicated in porphyria
Anti-psychotics	Indications for schizophrenia, bipolar disorder, irritability with autism spectrum disorder			Antipsychotics are sometimes used for their sedating properties in the context of other psychiatric behavior (e.g., mood, aggression). Due to their risk profile, antipsychotic use is not advised for the treatment of insomnia.
Over-the-Counter Medications and Dietary Supplements				
Diphenhydramine (e.g., Benadryl)	Label not for insomnia; used for adverse effect of sedation No FDA-approved indication	25-50 mg	-RCTs show short term efficacy	-Anticholinergic effects -Next day sedation -Routine use not recommended -Rapid tolerance to effects
Doxylamine (Unisom)	"For relief of occasional sleeplessness" No FDA-approved indication	50 mg	-EU RCT shows efficacy	-Caution with respiratory disorders and glaucoma or enlarged prostate gland -Avoid with sedatives, alcohol -Not intended for chronic use -Anticholinergic effects -Rapid tolerance to effects

Product (s) Name	Insomnia Indication Approval Year	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
Melatonin	"For temporary relief of fatigue, irritability, insomnia, and exhaustion." No FDA-approved indication	1 mg to 9 mg	-May be helpful for delayed sleep-wake phase syndrome/circadian sleep-wake rhythm disorder or with low levels of endogenous melatonin, such as in aging	-Not advised for long-term use -Nightmares

Abbreviations: AASM, American Academy of Sleep Medicine; BZD, benzodiazepine; CNS, central nervous system; CYP, cytochrome P450; DB, double blind; DDI, drug–drug interaction; MAOI, Monoamine oxidase inh bitors; N/A, not applicable; OSA, obstructive sleep apnea; PBO, placebo; PRN, as needed; RCT, randomized controlled study; W&P, warnings and precautions
Source: FDA Label or product package insert

Numerous hypnotic drugs have demonstrated effectiveness for the treatment of insomnia disorder, as suggested in Table 2. However, the risk-benefit profile may limit their use, particularly in special populations (e.g., children, elderly, pregnant women, patients with medical comorbidities).

Risks associated with hypnotics include daytime somnolence, drowsiness, fatigue, daytime driving impairment, cognitive impairment, dizziness, nausea, and headache [9]. Hypnotic drugs may be associated with tolerance, withdrawal, overdose, rebound insomnia, interaction with alcohol, and drug-drug interactions. Special populations such as those with lung disease, renal disorders, or the elderly are at increased risk for the adverse effects of sedatives and hypnotics [10]. More rarely, hypnotic drugs may be associated with new onset suicidal ideation, respiratory depression, and parasomnias, including complex sleep behaviors such as sleep driving. The 2015 update to the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults [11] notes that for elderly subjects, benzodiazepines and the non-benzodiazepine zolpidem are to be avoided. The reason stated was because the potential harms associated with the use of benzodiazepines and zolpidem to treat insomnia may outweigh the efficacy reported in studies of elderly populations.

Recently, the FDA acted on case reports of deaths from complex sleep behaviors reported to FDA Adverse Event Reporting System (FAERS). In April 2019, the FDA announced that several insomnia medications would require a new boxed warning for the label stating the following:

> Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of [TRADENAME]. Some of these events may result in serious injuries, including death. Discontinue [TRADENAME]. immediately if a patient experiences a complex sleep behavior. [12].

The FDA also issued a new contraindication to the label section for eszopiclone, zaleplon, and zolpidem to avoid use in patients who have previously experienced an episode of complex sleep behavior. Drugs approved more recently for the treatment of insomnia, such as melatonin agonists and an orexin receptor antagonist, appear to have a more favorable benefit to risk profile and currently do not include the warning associated with complex sleep behaviors.

Over-the-counter (OTC) medications and herbal remedies are also commonly used by patients. Melatonin and anti-histamines have at least some efficacy data, see Table 2 section on Over-the-Counter Medications and Dietary Supplements for details [9]. However, most remedies do not have supporting evidence. For example, a meta-analysis with 14 randomized trials found no significant difference between commonly used herbal medicines and placebo, including valerian root, chamomile, kava, and wuling.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lemborexant has not been approved or marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

- July 2011 - Initial IND 111871 for lemborexant submitted.
- November 2014 – Type B End of Phase 2 meeting. Agreement on proposed phase 3 program supporting proposed insomnia indication, including total subject exposures, proposed doses and overall number of enrolled elderly subjects, plus agreement on proposed approach for rebound insomnia, measures to assess residual sleepiness and assessment of cataplexy via an adjudication committee.
    - Confirmation that Eisai would be incorporating an assessment of bone toxicity in the pre-post-natal development study in the rat including calcium, phosphorus, iron, histopathology and bone length – resolved February 2015
    - Agreement with the approach to analyze adverse events related to drug abuse liability and with the proposed customized MedDRA queries related to abuse liability
- April 2015 – Agreed iPSP sent to the Applicant indicating initial agreement with full waiver of pediatric assessment.
- April 2015 - Metabolite M10 appears to be adequately qualified in nonclinical species. However, Eisai still needs to provide area under the curve (AUC) values for all major metabolites in rats and monkeys at steady state.
- May 2015 – Type C written response only. Agreements on proposed revisions to phase 3 program and clinical and nonclinical components of the development program for the filing of the NDA.
- July 2015 – Agreement from Division that a separate thorough QT study would not be necessary with NDA filing.
- November 2016, correspondence - Additional information about abuse-related AEs would be collected for specific analyses related to abuse potential in the phase 3 program.
- February 2017 – Type C written response only. Guidance provided to the Applicant on drug abuse, dependence, withdrawal and diversion terms that should trigger individual subject narratives.
- April 2017, correspondence. Applicant agrees to have cataplexy and seizure events adjudicated by an independent committee. Applicant modifies ongoing protocols to include instructions to ask about falls at very visit.
- June 2018 – Type B pre-NDA meeting. Agreements on proposed data cut, pooling strategy, summaries of adverse events, and aspects of statistical analysis plans.
- December 27, 2018 – NDA package submitted.

3.3. Foreign Regulatory Actions and Marketing History

Lemborexant has not been approved or marketed in any other country.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The site data for the primary efficacy studies 303 and 304 was reviewed with the clinical team, statistical team, and Office of Scientific Investigations (OSI) reviewer Roy Blay, Ph.D. The OSI team reported that the studies (Protocols E2006-G000-303 and E2006-G000-304) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

Site 4102, Study 304: Dr. Garcia-Borreguerro's site in Madrid, Spain, was selected for inspection because of its relatively large enrollment and particularly strong efficacy results in favor of the drug. At site 4102, 60 subjects were screened, 48 subjects were randomized into the study, and 12 subjects were screen failures. No deficiencies were observed in the review of the informed consent forms for all screened subjects. The primary and secondary endpoints were verifiable with no under-reporting of adverse events noted. The inspection concluded no action indicated (NAI).

Site 5002, Study 303: Dr. Harper's site was selected for inspection because of its relatively large enrollment and unusually high dropout rate (60%). At site 5002, 83 subjects were screened, 32 subjects were enrolled, 16 subjects discontinued the study, and 16 subjects completed the study. There were no deficiencies observed. The primary endpoints were verifiable with no under-reporting of adverse events noted. The inspection concluded no action indicated (NAI).

Site 4006, Study 304: Dr. Safirstein's site was selected for inspection because of its relatively large enrollment and a higher rate of dropouts as compared to other sites with similar enrollment numbers. At site 4006, 159 subjects were screened, 58 subjects were randomized into the study, and 53 subjects completed the study. Primary and prespecified secondary polysomnogram (PSG) parameters were verified for all subjects. Site The inspection concluded voluntary action indicated (VAI) and a form FDA 483 was issued because of subjects being enrolled who met exclusion criteria. One case was for a female of child-bearing potential who was enrolled and received study drug. The issue was reported to the Sponsor and IRB and resulted in retraining of the staff as a corrective action. Two enrolled subjects had missing values on exclusionary criteria (previous participation in trials, HIV status), yet were not reported as protocol deviations. Dr. Blay reported that, as a corrective action, Dr. Safirstein will appoint an individual responsible for data quality control for each future study to prevent similar omissions of source data and she will conduct periodic reviews.

Additional details of Dr. Blay's report are in the Clinical Inspection Summary.

4.2. Product Quality

The Office of Product Quality (OPQ) Quality Assessment team reviewed data related to chemistry, manufacturing and controls (CMC) for this NDA. Please refer to the Quality Assessment teams Executive Summary for the full report provided by OPQ for full details. In brief, the team stated that applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. All facilities are in good standing. The team notes that Eisai studied three different formulations in clinical studies. The tablet (b) (4) for the formulations used in phase 2 and phase 3 studies was the same but a different (b) (4) was used for the phase 3 studies.

The drug product used in the phase 3 clinical drug development program is the same as proposed commercial product.

4.3. Clinical Microbiology

There were no clinical microbiology issues applicable to this review.

4.4. Devices and Companion Diagnostic Issues

There were no devices and companion diagnostic issues applicable to this review.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical studies conducted with lemborexant, and submitted with the NDA, are adequate to assess the safety of lemborexant for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The established pharmacologic class for lemborexant is an orexin receptor antagonist. In vitro, lemborexant bound with high affinity to orexin-1 and orexin-2 receptors, with a higher affinity for orexin-2, IC_{50} values of 6.1 nM and 2.6 nM, respectively. Lemborexant functions as a competitive antagonist at both receptors with slightly higher activity at the orexin-2 receptor compared to the orexin-1 receptor. Suvorexant, an FDA-approved orexin receptor antagonist for the treatment of insomnia, was used as a comparator in several of the Applicant's in vitro pharmacology studies. In these assays, suvorexant similarly bound to orexin-1 and orexin-2 receptors; however, in contrast to lemborexant, it displayed slightly greater affinity and functional activity at the orexin-1 receptor versus the orexin-2 receptor, and also displayed slower receptor on/off kinetics compared to lemborexant. Oral administration of lemborexant to mice and rats significantly increased total sleep time, without an effect on the REM sleep ratio, with an ED_{50} of 1 mg/kg and 4.4 mg/kg, respectively. Oral doses up to 30 mg/kg to preproorexin knockout mice, in which the orexin pathway is dysfunctional, and to orexin neuron-deficient transgenic mice, did not induce sleep, demonstrating that lemborexant acts through the orexin signaling pathway to exert its sleep-promoting effects in mice. Daily treatment of lemborexant for three consecutive weeks to rats did not lead to tolerance of lemborexant's sleep promoting effects or result in a rebound effect after dosing cessation, in contrast to the nonbenzodiazepine drug, zolpidem.

Nine metabolites found in human plasma (M3, M4, M7, M8, M9, M10, M13, M14, and M15) have affinity to human orexin-1 and orexin-2 receptors in vitro. M10, the only major human metabolite, displayed binding affinities comparable to lemborexant, with IC_{50} values of 4.2 and 2.9 nM at the human orexin-1 and orexin-2 receptor, respectively. Neither lemborexant or its metabolites (M4, M9, or M10) are strong inhibitors of the hERG channel, IC_{50} values of 6.1, 5.2, 11.2, and 9.0 µM, respectively. Lemborexant prolonged the QTc interval in conscious telemetered monkeys after single doses ≥30 mg/kg, which produces exposures approximately 22-fold the steady state C_{max} value in humans at the maximum recommended human dose (MRHD). There were no drug-related effects on any other cardiovascular parameters in monkeys or in conscious dogs after single oral doses of lemborexant. Lemborexant, at an oral dose up to 1000 mg/kg in male rats, did not have any effects on CNS or respiratory functions in a combined safety pharmacology study. In a mouse model of emotion-induced cataplexy, lemborexant in combination with a strong emotional stimulus (chocolate), increased cataplexy type behaviors in mice. A similar finding was observed in dogs treated with the orexin receptor antagonist, suvorexant, and is described in the drug label.

Lemborexant has relatively low oral bioavailability in male rats and monkeys that increases slightly with increasing dose, up to 23%. Lemborexant has non-linear pharmacokinetics (PK) in rats after single and repeated dosing and T_{max} increases with increasing dose from 0.25 to 4.5 hours. PK is roughly linear in monkeys with T_{max} values ranging from 1.0 to 1.5 hours. The elimination half-life ($t_{1/2}$) is slightly longer in male monkeys compared to male rats after single oral doses, approximately 2 to 3 hours in rats and 4 to 5 hours in monkeys. Plasma exposure to lemborexant is greater in female rats compared to male rats at equivalent doses. There is no significant sex difference in exposure in monkeys. Drug accumulation is evident after repeat dosing to rats and monkeys, up to a 4-fold increase in exposure. Lemborexant is rapidly and extensively distributed to tissues in rats and monkeys with the highest levels found in liver and no accumulation in melanin-containing tissues in rats. Lemborexant and its metabolites readily cross the blood brain barrier and drug concentrations in cerebral spinal fluid are higher than that of plasma. Similarly, lemborexant and its metabolites are found in milk of lactating rats at concentrations higher than those in plasma. Lemborexant is highly bound to plasma proteins, >82% across multiple species and was highest in human plasma. There are species differences in plasma protein binding of lemborexant metabolites, with the highest level of binding observed in human plasma. Lemborexant is metabolized primarily by CYP3A4 and to a lesser extent by CYP3A5 to form several metabolites in rats, monkeys, and humans; however M10 is the only major human metabolite found at levels of 12.5% of total drug related material in plasma. Plasma exposure to M10 in rats, dogs, and rabbits at dose levels used in the chronic toxicity studies, embryofetal development studies, and the rat 2-year carcinogenicity study are higher than exposures in humans at the MRHD of 10 mg. Therefore, metabolite M10 has been adequately qualified in nonclinical studies. Defluorinated metabolites are detected in the liver and excreta of rats and excreta of monkeys, suggesting that oxidative defluorination is one of the metabolic pathways of lemborexant in rats and monkeys. No defluorinated metabolites are found in human plasma, urine, or feces as measured in a human mass balance study with [^{14}C]E2006. Additionally, no human specific metabolites have been identified. Lemborexant is predominantly excreted in feces in rats, monkeys, and humans.

The general toxicity of orally administered lemborexant at doses up to 1000 mg/kg/day was evaluated in rats and monkeys up to 6 months and 9 months in duration, respectively. In rats, drug-related deaths occurred at the highest dose. Increased liver weights were observed at ≥100 mg/kg/day, with corresponding hepatocellular hypertrophy at the highest dose indicative of increased liver metabolizing enzymes. Adverse bone toxicity (histologic bone structural changes, decreased bone mineral density, and bone fractures) and teeth toxicity (tooth discoloration and histologic changes in ameloblasts) was observed following daily oral administration for 13 weeks or greater at doses ≥100 mg/kg/day, which is approximately 129 times the MRHD based on AUC. These findings correlated with decreased serum calcium and serum iron and increases in urine fluoride excretion and bone fluoride accumulation. Non-adverse teeth discoloration and bone pigmentation was observed at all dose levels in rats without any structural changes at the lowest dose of 30 mg/kg/day. Similar non-adverse pigmentation of bone and teeth was observed in rats at all doses, as low as 10 mg/kg/day, in the 2-year carcinogenicity, which produced plasma exposure levels of lemborexant

approximately 8 and 2 times the MRHD based on AUC in male and female rats, respectively. The NOAEL in male and female rats is 100 and 30 mg/kg/day which are 41 times and 12 times the MRHD based on AUC, respectively. No NOEL was identified for pigmentation of bone and teeth in rats. Females had higher plasma exposures than males at equivalent doses.

In monkeys, the predominant finding in all general toxicity studies is gastro-intestinal (GI)-related clinical signs including feces changes and vomiting and CNS-related clinical signs of decreased activity and somnolence which are attributed to the pharmacology of lemborexant. Changes in hematology parameters were also observed which correlated with alteration of iron metabolism and microscopic findings of increased hemosiderin in the spleen and bone marrow and increased hematopoiesis in bone marrow. Increased liver weights correlated with microscopic findings of increased hepatocellular hypertrophy. Adverse bone or teeth toxicity was not observed in monkeys; however, pigmentation of bone was observed in a few animals at the highest dose of 1000 mg/kg/day which produced exposures of lemborexant greater than 200 times the MRHD based on AUC. The pigmentation in the femur correlated with a dose-dependent increase in urinary fluoride excretion. The NOAEL for monkeys is 10 mg/kg/day, which is 12-times the MRHD based on AUC.

The observed bone and teeth toxicity in rats may be the result of fluorosis caused by the release of fluoride during the metabolism of lemborexant; an increase in fluoride levels was observed in bones of rats following daily administration of lemborexant. Lower amounts of fluoride in urine was observed in monkeys compared to rats, and no defluorinated metabolites were detected in human urine samples. The significance of the bone and teeth findings in animals to human risk appears to be very low.

Reproductive and developmental toxicity was assessed in fertility studies in male and female rats, embryo-fetal development studies in pregnant rats and rabbits, and a pre- and post-natal development study in rats. Irregular estrous cycles and decreased pregnancy rates were observed in female rats at doses ≥100 mg/kg/day. Based on findings in published literature, these effects may be related to the pharmacology of the drug and its effects on hormone regulation, specifically luteinizing hormone (LH); however, LH levels were not measured in any study with lemborexant. Additional findings at the high dose included a significant decrease in the number of corpora lutea, implantations, and live embryos. The NOAEL for effects on female fertility is 30 mg/kg/day, which is approximately 12 times the MRHD based on AUC. No effects on male fertility were observed with lemborexant at doses up to 1000 mg/kg/day, which are greater than 100 times the MRHD based on AUC. In pregnant rats treated orally with lemborexant, maternal toxicity consisting of decreased body weight and food consumption was observed at the highest dose of 600 mg/kg/day. Toxicities to fetuses were observed at this maternally toxic dose and included an increase in postimplantation loss and decrease in mean fetal weights, increased incidence of the external malformations cleft palate and omphalocele, increased incidence of visceral malformation of membranous ventricular septum defect, increase in skeletal variations including 14th cervical rib, and an increase in incomplete ossification. One fetus each at the low and mid dose also had membranous ventricular septum

defect. However, based on an additional study investigating the background incidence of membranous septum defect in the conducting laboratory and data from published literature, the incidence in the low and mid dose groups was determined to be within the historical/lab control background and therefore is not considered drug-related. The NOAEL is 200 mg/kg/day for maternal toxicity and embryofetal development findings, which is greater than 100 times the MRHD based on AUC. In pregnant rabbits, maternal toxicity was observed at the highest dose of 100 mg/kg/day which consisted of decreased body weight that correlated with decreased food consumption. Toxicities to fetuses were observed at this maternally toxic dose and included the skeletal variation of the presence of cervical ribs and the visceral variation of supernumerary lung lobes. The NOAEL is 30 mg/kg/day for maternal toxicity and embryofetal development in rabbits, which is approximately 23 times the MRHD, based on AUC. In a pre- and post-natal development study in rats treated with lemborexant during pregnancy and lactation, maternal toxicity consisting of a decrease in body weight gain and food consumption was observed at the highest dose of 300 mg/kg/day. At this dose, offspring body weights and femur lengths were significantly decreased indicating an adverse effect on pup growth and development. There was also a significant decrease in the acoustic startle response in pups from the high dose group. There were slight decreases in the bone biomarkers, total iron binding capacity and unsaturated iron binding capacity for pups from the high dose along with an increase in bone fluoride levels. The maternal and offspring NOAEL is 100 mg/kg/day, which is approximately 93 times the MRHD based on AUC.

Lemborexant was not genotoxic as tested in a standard and adequate genetic toxicology battery. Lemborexant did not increase the incidence of tumors in a 6-month carcinogenicity study in Tg ras H2 transgenic mice or in a 2-year study in rats and therefore is considered non-carcinogenic. The high doses used in the rat study are approximately ≥82 times the MRHD based on AUC.

Lemborexant is not phototoxic in vitro. The Applicant conducted an adequate assessment of all potentially genotoxic impurities. Genotoxic impurities would be controlled according to ICH M7. The specification limit of NMT (b) (4)% for the non-genotoxic impurity (b) (4) is acceptable from a nonclinical standpoint based on qualification in nonclinical toxicity studies.

An overall adequate nonclinical safety assessment of lemborexant was conducted to support the NDA for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, at a maximum recommended human dose of 10 mg. The NDA is approvable from a nonclinical standpoint.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3.Pharmacology

Primary Pharmacology

In Vitro Receptor Binding

Binding of lemborexant and suvorexant to human orexin-1 (OX1R) and orexin-2 receptors (OX2R) was determined in radiolabeled receptor binding assays using membrane fractions prepared from CHO cells expressing human OX1R or OX2R and [^{125}I]- Orexin-A as the radioligand (study no. M10032). In these in vitro assays, IC_{50} values were calculated for lemborexant at human OX1R and OX2R to be 6.1 nM and 2.6 nM, respectively. Binding IC_{50} values of suvorexant to the human OX1R and OX2R were calculated to be 8.8 nM and 12 nM, respectively. In vitro assays measuring the on and off kinetics of lemborexant at OX1R and OX2R receptors was evaluated in CHO cells expressing human OX1R or OX2R and [^{125}I]- Orexin-A and [^{3}H]EMPA as the radioligands, respectively (study nos. 1000026610 and M14007). Suvorexant was included as a comparator, but only in the OX2R assay. Lemborexant displayed fast association and dissociation to both OX1R and OX2R, and had faster kinetics than suvorexant at OX2R.

In Vitro Functional Assays

In a cell-based functional reporter enzyme assay using HEK-293 cells stably transfected with recombinant human or mouse OX1R and OX2R, lemborexant functioned as a competitive antagonist at both receptors, with K_i values of 14.1 nM and 0.391 nM at human OX1R and OX2R, respectively (study no. W-20110320). In a cell-based functional calcium mobilization assay using HEK-293 cells stably transfected with recombinant human, mouse, or rat OX1R and OX2R, lemborexant similarly acted as an antagonist at both receptors, with K_i values of 8.1 nM and 0.48 nM at OX1R and OX2R, respectively (study no. M16023). Suvorexant was included as a comparator in the calcium mobilization assay and similarly acted as an antagonist at both receptors, with Ki values of 1.4 nM and 2.2 nM at OX1R and OX2R, respectively. Lemborexant did not demonstrate agonist activity at OX1R or OX2R in either of the assays.

Table 3: In Vitro Properties of Lemborexant at Human OX1R and OX2R Compared to Suvorexant

Assay	Lemborexant		Suvorexant	
	hOX1R	hOX2R	hOX1R	hOX2R
Binding affinity	IC_{50}: 6.1 nmol/L	IC_{50}: 2.6 nmol/L	IC_{50}: 8.8 nmol/L K_i: 0.55 nmol/L[a]	IC_{50}: 12.0 nmol/L K_i: 0.35 nmol/L[a]
Binding kinetics	k_{on}: 0.0262 $L \cdot nmol^{-1} \cdot min^{-1}$	k_{on}: 0.0496 $L \cdot nmol^{-1} \cdot min^{-1}$	k_{on}: 0.049 $L \cdot nmol^{-1} \cdot min^{-1a}$	k_{on}: 0.0052 $L \cdot nmol^{-1} \cdot min^{-1}$ 0.00763 $L \cdot nmol^{-1} \cdot min^{-1a}$
	k_{off}: 0.244 min^{-1}	k_{off}: 0.0626 min^{-1}	k_{off}: 0.0085 min^{-1a}	k_{off}: 0.0164 min^{-1} 0.0078 min^{-1a}
Cell-based functional reporter enzyme assay	K_i: 14.1 nmol/L	K_i: 0.391 nmol/L	—	—
Cell-based calcium mobilization assay	K_i: 8.1 nmol/L 4.8 nmol/L	K_i: 0.48 nmol/L 0.61 nmol/L	IC_{50}: 49.9 nmol/L[a] K_i: 1.4 nmol/L	IC_{50}: 54.8 nmol/L[a] K_i: 2.2 nmol/L

hOX1R = human OX1R, hOX2R = human OX2R, IC_{50} = 50% inhibitory concentration, K_i = inhibition constant, k_{off} = dissociation rate constant, k_{on} = association rate constant, — = no data available.
a: Data from eCTD disclosed on the PMDA website (http://www.pmda.go.jp/PmdaSearch/iyakuSearch/).
Source: Study Nos. 100026610, M10032, M14007, M16023, and W-20110320; Beuckmann, et al., 2017.

Source: Applicant's table: Pharmacology Written Summary, p. 33

In Vivo

Activation of orexin-2 receptors produces increases in plasma ACTH levels in rats. Intracerebroventricular administration of [Ala^{11}, D-leu^{15}]-orexin-B peptide to male Fischer rats caused a statistically significant increase in plasma ACTH levels compared to PBS-injected rats. Pretreatment of rats with orally administered lemborexant (1, 3, 10, or 30 mg/kg) resulted in a dose dependent decrease in plasma ACTH levels compared to vehicle treated rats, suggesting that lemborexant inhibits activation of orexin-2 receptors (study no. W-20110223).

Lemborexant statistically significantly increased total sleep time in male C57BL/6 mice when orally administered at doses of 1 and 3 mg/kg as measured by EEG and EMG signals from implanted telemetry devices. In comparison, almorexant (a dual orexin receptor antagonist) at 30 mg/kg and zolpidem (a $GABA_A$ receptor positive modulator) at 3 and 10 mg/kg also significantly increased total sleep time. Lemborexant did not significantly decrease sleep latency, although there was a decreasing trend; in contrast zolpidem significantly decreased sleep latency at 3 and 10 mg/kg. Lemborexant did not affect the REM sleep ratio (REM sleep time/total sleep time), while zolpidem at 10 mg/kg significantly decreased the REM sleep ratio (study no. W-20100965). In a similar study using male Sprague-Dawley rats, lemborexant statistically significantly increased total sleep time with an oral ED_{50} of 4.4 mg/kg without any effect on the REM sleep ratio or an effect on direct transitions from wakefulness to REM sleep (sleep onset REM); in contrast zolpidem statistically significantly decreased the REM sleep ratio after an oral dose of 30 mg/kg (study no. M10037). In a study using male orexin neuron-deficient mice (C57BL/6 orexin/ataxin-3 Tg/+) lemborexant increased total sleep time only in the wild-type mice, suggesting lemborexant's effects act through the orexin pathway (study no. M12001). Oral administration of 30 mg/kg lemborexant to male Sprague-Dawley rats for 21 consecutive days did not result in tolerance to the sleep-promoting effects over the treatment period, as measured by total sleep time, non-rapid eye movement (REM) sleep time, and sleep

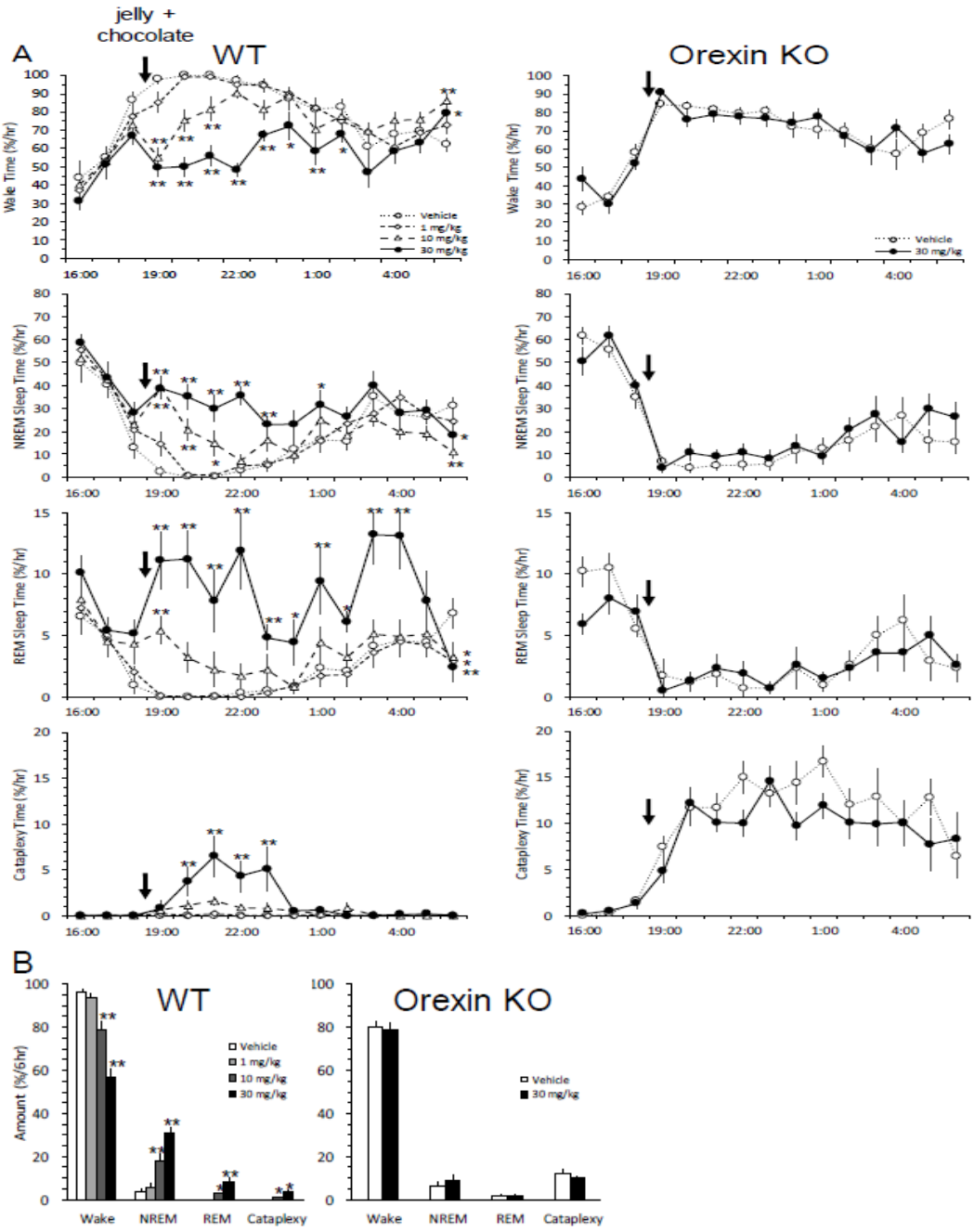
latency (study no. M10038). Additionally, there was no sign of any rebound effect (decrease in sleep parameters beyond the predose baseline values) following two days of dosing cessation. In contrast, after cessation of dosing of the reference compound, zolpidem (100 mg/kg), a rebound effect (an overshoot reduction of non-REM sleep) was observed in the mice.

Cataplexy

Study title/ study number: Evaluation of E2006 in a Mouse Model of Emotion-Induced Cataplexy/ W-20140712

Male C57 BL/6J wild-type (WT) mice and preproorexin knockout mice of C57 BL/6J genetic background (n=8) were implanted with EEG and EMG electrodes. 8 days after surgery, mice were given vehicle (0.5% methylcellulose) or lemborexant (1, 10, or 30 mg/kg) for WT and 30 mg/kg for KO mice, in a cross-over design. Vehicle and lemborexant were administered as a jelly mixed with 14% gelatin, 20% Splenda, and 4% natural flavor for voluntary eating in order to reduce stress induced by handling and gavage, which can reduce cataplexy. A piece of chocolate (Hershey's Kiss) was used as the strong emotional-stimulus and given to mice at the dark onset. Lemborexant in WT mice at 10 and 30 mg/kg dose-dependently and statistically significantly decreased the percent wake time, and increased the percent time in NREM and REM sleep, both with and without the chocolate stimulus. Co-administration of lemborexant (10 and 30 mg/kg) with chocolate statistically significantly increased the time spent in cataplexy in WT mice. Lemborexant had no effect on any sleep parameters, including cataplexy time, in the KO mice. The findings of this study will be reported in the animal toxicology section 13.2 of the drug label.

Figure 1: Effects of Lemborexant on Cataplexy in Wild-Type and Orexin Knock-Out Mice



Effects of chocolate on amount of sleep/wake and cataplexy in vehicle- or E2006-treated WT mice and orexin KO mice.

A: Hourly amounts of wake, NREM sleep, REM sleep and cataplexy in WT mice (left panels) and orexin KO mice (right panels). Arrows indicate the time of vehicle/drug jelly (at 18:45) and chocolate (at 19:00) presentation. **B:** Average amount of wake/NREM sleep/REM sleep/cataplexy for 6 hours after vehicle or E2006 administration. * $p<0.05$, ** $p<0.01$ compared to vehicle day.

Abbreviations: KO, knock-out; p-value, probability value; NREM, non–rapid eye movement; REM, rapid eye movement; WT, wild-type

Source: Applicant's table: NDA, study report W-20140712

Established Pharmacologic Class
Orexin receptor antagonist

Metabolite of Lemborexant
Nine of the twelve metabolites found in human plasma (M3, M4, M7, M8, M9, M10, M13, M14, and M15) displayed binding affinities at human orexin 1 and orexin 2 receptors comparable to lemborexant, as measured in a radioligand binding assay using CHO cells expressing either recombinant human OX1R or OX2R and radiolabeled ^{125}I-orexin-A peptide. IC_{50} values for the major human metabolite, M10, at the OX1R and OX2R were 4.2 and 2.9 nM, respectively (study no. M13009).

Secondary Pharmacology
Lemborexant (10 µM) did not significantly inhibited binding to a number of receptors, transporters, and ion channels, except for the human melatonin MT1 receptor (74% inhibition) (study no. 929062). However, in vitro lemborexant was found to function as an antagonist at the MT1 receptor with a K_i of 922 µM and therefore does not contribute to the efficacy of lemborexant (study no. M11009). Metabolites M4, M9, and M10 also significantly inhibited binding to the MT1 receptor at 10 µM (51%, 55%, and 71% inhibition, respectively) (study no. 100023762). Lemborexant had no effect on $GABA_A$-invoked chloride currents in an in vitro patch clamp assay using $GABA_A$ receptor-expressing cells (study no. W20110355). Lemborexant, up to 300 mg/kg administered orally to male mice, had no significant effect on ethanol-induced anesthesia duration or motor coordination and balance compared to vehicle-treated mice (study nos. W-20110180 and W-20110154).

Safety Pharmacology

Study/ Study no.	Findings
hERG channel assay/ SBL038-047 (GLP)	Lemborexant dose-dependently inhibited hERG potassium current, IC_{50} = 6.1 µM.
hERG channel assay/ W-20140611 (non-GLP)	Metabolites M4, M9, and M10 dose-dependently inhibited hERG potassium current, IC_{50} = 5.2, 11.2, and 9.0 µM, respectively.
CVS: monkeys conscious telemetered/ S10117 (GLP)	Single oral administration of 30 and 100 mg/kg lemborexant to male monkeys produced a statistically significant prolongation of the QTc (Bazett's correction) interval at 2 and 4 hours after dosing and lasted until 8 hours postdose. These doses of lemborexant produced plasma concentrations approximately 22-fold the steady state C_{max} value in humans at the maximum recommended human dose. There were no changes in other cardiovascular parameters that were considered drug-related.
CVS: monkeys conscious telemetered/ T11037 (non-GLP)	When administered approximately 0.5 hours before lights-out, single oral administration of lemborexant at 100 mg/kg produced a statistically significant prolongation of the QTc interval at 4 hours postdose. This dose of lemborexant produced plasma concentrations approximately 35-fold the steady state C_{max} value in humans at the maximum recommended human dose. There were no changes in other cardiovascular parameters that were considered drug-related.
CVS: anesthetized dogs/ W-20110322 (non-GLP)	Single I.V. administration of ≥1 mg/kg lemborexant to anesthetized dogs resulted in shortening of the PQ interval, increased heart rate, and decreased mean aortic pressure, which produced plasma concentrations >10-fold the steady state C_{max} value in humans at the maximum recommended human dose.
CVS: conscious dogs/ W-20110279 (non-GLP)	No effects on heart rate, blood pressure, and ECG parameters in dogs up to single oral doses of 30 mg/kg; GI-related clinical signs including vomiting occurred in all drug-treated animals.
CNS: rats/ S10120 (GLP)	No effects on CNS functions in male Sprague-Dawley rats up to 1000 mg/kg as measured by FOB methods in an extended single-dose oral toxicity study.
Respiratory: rats/ S10120 (GLP)	No effects on respiratory function in male Sprague-Dawley rats up to 1000 mg/kg in an extended single-dose oral toxicity study.

5.4.ADME/PK

Type of Study

Major Findings

Absorption

Rat (study no. 16-561)

Table 4: Lemborexant Pharmacokinetic Parameters After Single Intravenous and Oral Administration to Male Rats

Pharmacokinetic Parameters	IV Administration		PO Administration		
	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
C_{max} (ng/mL)	NA	NA	50.0±32.6	452±324	964±180
t_{max} (h)	NA	NA	0.25 (0.25 – 1.00)	1.00 (1.00 – 2.00)	4.50 (1.00 – 8.00)
$AUC_{(0-t)}$ (ng·h/mL)	109±10	351±40	86.4±37.8	1150±710	7960±1760
$AUC_{(0-inf)}$ (ng·h/mL)	110±9	353±41	87.8±37.6	1160±710	7970±1750
$t_{1/2}$ (h)	1.61±0.17	1.64±0.19	1.49±0.26	2.65±1.16	2.24±0.13
$MRT_{(0-inf)}$ (h)	1.53±0.28	1.19±0.30	1.89±0.24	2.95±1.01	6.70±0.71
CL (mL/h/kg)	2730±240	2870±330	NA	NA	NA
V_{ss} (L/kg)	4.21±1.12	3.40±0.98	NA	NA	NA
F (%)	NA	NA	2.5	11.0	22.6

The mean and SD of 4 individual values are presented for the pharmacokinetic parameters except t_{max} and F. For t_{max}, the median and range for 4 individual values are presented. F values were calculated using the mean AUC values.

$AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CL = total plasma clearance, F = absolute bioavailability, IV = intravenous, $MRT_{(0-inf)}$ = mean residence time from zero time extrapolated to infinite time, NA = not applicable, PO = oral, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life, V_{ss} = volume of distribution at steady state.

Source: Applicant's table: Pharmacokinetics Written Summary, p. 13

Monkey (study no. 16-562)

Table 5: Lemborexant Pharmacokinetic Parameters After Single Intravenous and Oral Administration to Male Monkeys

Pharmacokinetic Parameters	IV Administration		PO Administration		
	0.3 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
C_{max} (ng/mL)	NA	NA	61.7±41.2	110±65	660±404
t_{max} (h)	NA	NA	1.50 (1.00 – 2.00)	1.00 (1.00 – 2.00)	1.50 (1.00 – 2.00)
$AUC_{(0-t)}$ (ng·h/mL)	244±34	840±90	166±61	411±194	2010±850
$AUC_{(0-inf)}$ (ng·h/mL)	251±30	852±97	169±62	420±200	2020±850
$t_{1/2}$ (h)	6.25±3.63	5.16±0.49	3.78±2.34	5.23±1.21	5.10±1.55
$MRT_{(0-inf)}$ (h)	3.78±1.88	2.82±1.03	3.81±1.47	4.74±1.01	4.22±1.32
CL (mL/h/kg)	1210±130	1190±130	NA	NA	NA
V_{ss} (L/kg)	4.73±2.58	3.31±1.17	NA	NA	NA
F (%)	NA	NA	19.8±7.0	16.1±7.0	23.4±8.5

The mean and SD of 4 individual values are presented for the pharmacokinetic parameters except t_{max}. For t_{max}, the median and range for 4 individual values are presented.

$AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CL = total plasma clearance, F = absolute bioavailability, IV = intravenous, $MRT_{(0-inf)}$ = mean residence time from zero time extrapolated to infinite time, NA = not applicable, PO = oral, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life, V_{ss} = volume of distribution at steady state.

Source: Applicant's table: Pharmacokinetics Written Summary, p. 16

Distribution

Protein binding (study nos. 12-304, 16-559, DMPKT2017-003)

Table 6: In Vitro Plasma Protein Binding of Lemborexant and Its Metabolites

Species	Lemborexant	M4	M9	M10
Mouse	87%	66%	74%	68%
Rat	82%	56%	75%	65%
Monkey	83%	65%	77%	85%
Human	89%	74%	86%	92%

Note: Values represent highest percent binding from three concentrations tested (100, 300, and 1000 ng/ml).

Lemborexant has a higher affinity for human low-density lipoprotein (LDL; 79% bound), human serum albumin (HSA; 74% bound), and high-density lipoprotein (HDL; 71% bound), compared to α-acid glycoprotein (α1-AGP; 13% bound) and human □-globulin (HG; 9% bound). There is no concentration dependency in plasma protein binding of lemborexant and its metabolites in all animal species tested and humans.

CSF (study no. 16-561, 16-562)

Lemborexant and its metabolites (M4, M9, and M10) rapidly crosses the blood-brain-barrier as concentrations of each were found in cerebral spinal fluid (CSF) of male rats and male monkeys by 1 hour after a single oral administration of 100 mg/kg and 10 mg/kg lemborexant, respectively. In male rats at steady state, CSF to unbound plasma concentration ratios ranged from 0.513 to 0.558 for lemborexant, 0.429 to 0.442 for M9, 0.212 to 0.228 for M10, and 0.147 to 0.160 for M4. In male monkeys at steady state, CSF to unbound plasma concentration ratios ranged from 0.493 to 1.08 for lemborexant, 0.632 to 0.947 for M10, 0.570 to 0.824 for M9, and 0.419 to 0.509 for M4. These data indicate a differential distribution of metabolites to CSF in rats and monkeys, e.g. more parent drug than metabolites in CSF of rats and monkeys.

Tissue: rat and monkey (study nos. 14-074, 14-188, 14-075)

[^{14}C]lemborexant is rapidly and widely distributed to tissues after a single oral administration (10 mg/kg) to male Sprague-Dawley rats. Peak radioactivity was reached in tissues by the first time point of 1 hour, except for the cecum and large intestine which reached peak concentrations at 8 hours post-dose, and rapidly decreased from all tissues. The liver has the highest distribution of radioactivity, followed by the stomach, cecum, small and large intestines. Concentrations of radioactivity in the sciatic nerve, abdominal aorta, blood cells, mesenteric lymph node, pancreas, renal cortex, adrenal gland, kidney, Harderian gland, fat, brown fat, small intestine, and liver were higher than that in plasma, while concentrations of radioactivity in the eyeball, cerebellum, cerebrum, medulla oblongata, and spinal cord were less than that in plasma. Similar tissue distribution of [^{14}C]lemborexant was observed in pigmented brown rats and no accumulation was observed in melanin-containing tissues (skin and eyeball).

Type of Study	Major Findings
	[^{14}C]lemborexant also rapidly (by 1 hour post-dose) distributed to tissues of male cynomolgus monkeys after a single oral administration (3 mg/kg), with the highest levels of radioactivity observed in bile in the gallbladder followed by the liver.
Metabolism In vivo: rats, monkeys, human plasma (study no. AE-7433-G, AE-7077-G, AE-7078-G, DMPKT2013-005)	The major metabolic pathways of lemborexant in rats and monkeys were oxidation of the dimethylpyrimidine or the fluorophenyl moiety of lemborexant and subsequent further oxidation or glutathione conjugation of metabolites in rats and subsequent sulfation or glucuronidation of metabolites in monkeys. Defluorinated metabolites were detected in the liver and excreta of rats and excreta of monkeys, suggesting that oxidative defluorination was one of the metabolic pathways of lemborexant in rats and monkeys. Lemborexant was the dominant component found in human plasma, accounting for 26.5% of total drug-related exposure. M10, M9, M4, and M18 (glucuronide of M3) were also detected as the major circulating components in plasma, accounted for 12.5%, 6.6%, 6.3%, and 6.0% of total drug-related exposure, respectively. M10 is therefore the only metabolite designated a major metabolite because it represented more than 10% of total drug-related exposure. M10 is formed in plasma of mice, rats, and monkeys. Plasma exposure levels of M10 observed in rats and monkeys at the highest dose levels of lemborexant used in the chronic repeat-dose toxicity studies, rat carcinogenicity study, and in females in the reproductive and development toxicity studies are equivalent to or higher than exposures of M10 observed in humans at the maximum recommended human dose of lemborexant (10 mg). Therefore, M10 is adequately qualified in nonclinical species. *See appendix for M10 exposure data in animals from toxicity studies compared to humans.* No defluorinated metabolites were found in humans, unlike in rats and monkeys. No human specific metabolites were identified in vivo.
In vitro: (study no. C12062, DMPKT2012-005, DMPKT2013-011, DMPKT2017-002, DMPKT2011-014)	Lemborexant is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5. Ten metabolites were detected in vitro in liver microsomes from mice, rats, monkeys, and humans and no human specific metabolites were identified. M1, M3, M5, M7, M8, and M9 were hydroxylated forms of lemborexant, M2, M4, and M10 were N-oxidated forms, and M6 was an oxidized form.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Excretion
Urinary and fecal (study no. 14-074, 14-075)

Placental transfer and breast milk (study no. AE-7524-G)</td><td>

Table 7: Excretion of Radioactivity After a Single Oral Administration of [^{14}C]Lemborexant to Male Rats and Monkeys

<table>
<tr><th>Data Source</th><th>Species
Dose</th><th colspan="3">Cumulative Excretion</th></tr>
<tr><td rowspan="3">Study No. 14-074</td><td rowspan="3">Sprague Dawley Rat
10 mg/kg</td><td colspan="3">Cumulative Excretion of Radioactivity up to 168 Hours (% of dose)</td></tr>
<tr><td>Urine</td><td>Feces</td><td>Total</td></tr>
<tr><td>5.9</td><td>90.6</td><td>96.5</td></tr>
<tr><td rowspan="3">Study No. 14-075</td><td rowspan="3">Cynomolgus Monkey
3 mg/kg</td><td colspan="3">Cumulative Excretion of Radioactivity up to 336 Hours (% of dose)</td></tr>
<tr><td>Urine</td><td>Feces</td><td>Total</td></tr>
<tr><td>22.5</td><td>75.1</td><td>97.5</td></tr>
<tr><td rowspan="3">Study No. 14-074</td><td rowspan="3">Sprague Dawley Rat[a]
10 mg/kg</td><td colspan="3">Cumulative Excretion of Radioactivity up to 48 Hours (% of dose)</td></tr>
<tr><td>Bile</td><td>Urine</td><td>Feces</td></tr>
<tr><td>100.0</td><td>1.1</td><td>1.2</td></tr>
</table>

Values represent the mean values of 3 animals.

a: Bile duct-cannulated rat.

Source: Applicant's table: Pharmacokinetics Written Summary, p. 56

Radioactivity was detected in fetuses from rats that were administered a single oral dose of 10 mg/kg [^{14}C]lemborexant on GD13, indicating that lemborexant crosses the placenta. After a single oral dose of 10 m/kg [^{14}C]lemborexant to pregnant rats on GD18, radioactivity concentrations in fetal liver, fetal digestive tract, fetal kidney, fetal heart, fetal lung, fetal plasma, fetal brain, and fetal blood were 0.85 to 0.51 times the maternal plasma concentration. Lemborexant and its metabolites (M3 and M9) are excreted in milk of lactating rats. The amount of radioactivity was higher in milk than plasma (AUC milk/plasma ratio of 3; C_{max} ratio of 6) from pregnant lactating rats that were administered a single oral dose of 10 mg/kg [^{14}C]lemborexant on postnatal day 10.

Table 8: Radioactivity In Plasma and Milk of Pregnant Lactating Rats

Parameter	Plasma	Milk
C_{max} (ng eq./ml)	734	4240
T_{max} (h)	0.25	0.25
$AUC_{(0\text{-inf.})}$ (ng eq. h/ml)	7830	22700
$T_{1/2}$ (h)	16.9	17.3

Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from 0 to infinity; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $T_{1/2}$, half life

</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>TK data from general toxicology studies

Rat: 13/26-week oral toxicity study (study no. K12033)
• Samples collected from satellite animals on days 1, 92 and 183 before dosing and 0.5, 1, 2, 4, 8, and 24 hours after dosing.

Monkey: 39-week oral toxicity study (study no. 6700074)
• Samples collected from main study animals on days 1, 85 and 269 before dosing and 1, 2, 4, 8, and 24 hours after dosing.</td><td><u>Rat</u>

Table 9: TK of Lemborexant in Rats on Day 183
<table>
<tr><td>Dose (mg/kg/day)</td><td>C_{max} (ng/ml) M/F</td><td>$AUC_{(0-24h)}$ (ng.h/ml) M/F</td></tr>
<tr><td>30</td><td>690/1543</td><td>2330/5335</td></tr>
<tr><td>100</td><td>2597/5230</td><td>18015/26486</td></tr>
<tr><td>1000</td><td>4798/13906</td><td>60697/240344</td></tr>
</table>
Abbreviations: AUC_{0-24h}, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; F, female; M, male; NOAEL, no observable adverse effect level; TK, Toxicokinetics; T_{max}, time to maximum plasma concentration
Note: Accumulation: Increase in C_{max} and AUC (1.4- to 3.8-fold) after repeated dosing for females at all doses levels and for males at 30 and 100 mg/kg/day only. Steady state mostly reached by day 92. T_{max} occurred between 1 and 2.5 hours at 30 and 100 mg/kg/day and between 6 and 24 hours at 1000 mg/kg/day.
NOAEL (bold) is 100 mg/kg/day for males and 30 mg/kg/day for females.

<u>Monkey</u>

Table 10: TK of Lemborexant in Monkeys on Day 269
<table>
<tr><td>Dose (mg/kg/day)</td><td>C_{max} (ng/ml) M/F</td><td>$AUC_{(0-24h)}$ (ng.h/ml) M/F</td></tr>
<tr><td>10</td><td>960/1160</td><td>5510/4970</td></tr>
<tr><td>100</td><td>6930/8660</td><td>82900/82800</td></tr>
<tr><td>1000</td><td>9620/6930</td><td>155000/98200</td></tr>
</table>
Abbreviations: AUC_{0-24h}, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; NOAEL, no observable adverse effect level; TK, Toxicokinetics; T_{max}, time to maximum plasma concentration
Note: Accumulation: Increase in C_{max} and AUC 1.8- to 4.2-fold) after repeated dosing for males and females.
T_{max} occurred between 1 and 8 hours and increased with increasing dose.
No consistent sex difference in exposure
NOAEL is 10 mg/kg/day for males and females.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>TK data from reproductive toxicology studies
<u>Rat</u>: embryo-fetal development (study nos. K12010, K12080)
• Samples collected from satellite animals on GD17 before dosing and 0.5, 1, 2, 4, 8, and 24 hours after dosing.

<u>Rabbit</u>: embryo-fetal development (study no. K12011)
• Samples collected from 5 animals on GD20 before dosing and 0.5, 1, 2, 4, 8, and 24 hours after dosing.

<u>Rat</u>: Pre- and Postnatal development (study no. 20060760)
• Samples from collected from satellite animals on GD17 before dosing and 0.5, 1, 2, 4, 8, and 24 hours after dosing.</td><td>Table 11: TK of Lemborexant In Pregnant Rats
<table>
<tr><th>Dose (mg/kg/day)</th><th>C_{max} (ng/ml)</th><th>$AUC_{(0\text{-}24h)}$ (ng.h/ml)</th></tr>
<tr><td>20</td><td>647</td><td>2845</td></tr>
<tr><td>60</td><td>2006</td><td>25529</td></tr>
<tr><td>200</td><td>4770</td><td>62870</td></tr>
<tr><td>600</td><td>10476</td><td>171321</td></tr>
</table>
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; NOAEL, no observable adverse effect level; TK, Toxicokinetics; T_{max}, time to maximum plasma concentration
Note: T_{max} is 0.5h at 20 and 60 mg/kg/day and increased to 8h at 200 and 600 mg/kg/day.
NOAEL is 200 mg/kg for maternal and embrofetal toxicity

Table 12: TK of Lemborexant in Pregnant Rabbits
<table>
<tr><th>Dose (mg/kg/day)</th><th>C_{max} (ng/ml)</th><th>$AUC_{(0\text{-}24h)}$ (ng.h/ml)</th></tr>
<tr><td>10</td><td>528</td><td>2904</td></tr>
<tr><td>30</td><td>1684</td><td>10017</td></tr>
<tr><td>100</td><td>5746</td><td>61388</td></tr>
</table>
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; NOAEL, no observable adverse effect level; TK, Toxicokinetics; T_{max}, time to maximum plasma concentration
Note: T_{max} is 0.5 h at 10 and 30 mg/kg/day and 1 h at 100 mg/kg/day.
NOAEL is 30 mg/kg for maternal and embryofetal toxicity

Table 13: TK of Lemborexant in Pregnant Rats
<table>
<tr><th>Dose (mg/kg/day)</th><th>C_{max} (ng/ml)</th><th>$AUC_{(0\text{-}24h)}$ (ng.h/ml)</th></tr>
<tr><td>30</td><td>947</td><td>6448</td></tr>
<tr><td>100</td><td>3150</td><td>40833</td></tr>
<tr><td>300</td><td>5625</td><td>90718</td></tr>
</table>
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; NOAEL, no observable adverse effect level; TK, Toxicokinetics; T_{max}, time to maximum plasma concentration
Note: T_{max} increased with increasing dose (2h, 4h, and 6h, respectively at 30, 100, and 300 mg/kg/day).
NOAEL is 100 mg/kg/day for maternal and offspring toxicity</td></tr>
<tr><td>TK data from Carcinogenicity study
E2006: An Oral Carcinogenicity Study in Rats K13092</td><td>Table 14: TK of Lemborexant in Rats on Day 178 of Carcinogenicity Study
<table>
<tr><th><u>Dose (mg/kg/day)</u></th><th><u>Male $AUC_{(0\text{-}24h)}$ (ng.hr/ml)</u></th><th><u>Female $AUC_{(0\text{-}24h)}$ (ng.hr/ml)</u></th></tr>
<tr><td><u>10</u></td><td><u>-</u></td><td><u>916</u></td></tr>
<tr><td><u>30</u></td><td><u>3574</u></td><td><u>7516</u></td></tr>
<tr><td><u>100</u></td><td><u>32185</u></td><td><u>48270</u></td></tr>
<tr><td><u>300</u></td><td><u>36034</u></td><td><u>-</u></td></tr>
</table>
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; MRHD, maximum recommended human dose of 10 mg; TK, Toxicokinetics; -, not tested
Note: No statistically significant tumor findings in male or female rats. Exposure at 300 males and 100 mg/kg/day females is >82 times the exposure at the MRHD.</td></tr>
</table>

Note: human AUC at steady state of 441 ng.hr/ml

5.5. Toxicology

5.5.1. General Toxicology

Pharmacology Reviewer Comments: *The conducting laboratories were different for the 13/26-week rat study and 39-week monkey study. Different drug substance lots, with different impurity profiles, were also used in the single-dose, 4-week, 13-week, and 13/26-week and 39-week rat and monkey studies. The dose selection was not optimal for the monkey studies with large multiples (10-fold) between the mid and high dose of 100 and 1000 mg/kg/day.*

Study title/ study number: E2006: A 39-Week Oral Toxicity Study in Monkeys/ 6700074

- MD and HD: GI-related clinical signs, changes in hematology parameters which correlated with alteration of iron metabolism and microscopic findings of increased hemosiderin in the spleen and bone marrow and increased hematopoiesis in bone marrow. Increased liver weights correlated with microscopic findings of increased hepatocellular hypertrophy
- HD: Pigmentation in the femur
- Dose-dependent increase in urinary fluoride excretion
- NOAEL is 10 mg/kg/day, which is 12-times the MRHD based on AUC

Conducting laboratory and location: (b) (4)

Histopathology examination: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 100, 1000 mg/kg/day once daily for 39 weeks. Doses selected based on 4-week and 13-week studies; NOAEL of 30 mg/kg/day, MTD of 1000 mg/kg/day due to GI-related clinical signs (see reviews under general toxicology; additional studies section below).
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Monkey/cynomolgus from (b) (4)
Number/Sex/Group:	4
Age:	At dosing initiation: 31-43 months old
Satellite groups/ unique design:	NA
Deviation from study protocol affecting interpretation of results:	No

Table 15: Observations and Results: Changes From Control

Parameters	Major findings
Mortality	None
Clinical Signs	Gastro-intestinal-related signs (feces changes, vomiting, and material found in cage or tray) were observed in MD and HD males and females sporadically throughout the study duration. Decreased activity and somnolence were observed in all drug-treated animals and were attributed to the pharmacological activity of the drug. Test Item-Related Clinical Observations: Incidence of Affected Animals

Dose (mg/kg): Sex	0		10		100		1000	
	Male	Female	Male	Female	Male	Female	Male	Female
Decreased activity	1(1)	-	9(4)	13(4)	22(4)	22(4)	32(4)	25(4)
Somnolence[a]	-	-	35 (4)	40 (4)	27 (4)	19 (4)	27 (4)	16 (4)
Feces soft	-	4(2)	-	1(1)	16(3)	1(1)	14(3)	22(2)
Feces liquid	-	-	1(1)	-	17(4)	2(2)	3(3)	59(4)
Material in cage or tray	1(1)	-	-	1(1)	20(4)	14(3)	55(4)	12(3)
Vomitus in cage or tray	-	-	2(1)	1(1)	10(4)	6(1)	17(2)	7(3)

A dash (-) indicates absence of finding in group.
Data are expressed as the total number of occurrences/group (number of animals affected).
[a] Due to a specific, pharmacologically-mediated clinical sign, somnolence (the animal's activity is decreased but upon external stimuli, the animal reacts normally) was used as of Day 14/13 instead of decreased activity.

Source: Applicant's study report 6700074 table: NDA 212028

Body Weights	No statistically significant, dose dependent effects for males or females; some small increases noted in LD and MD groups relative to corresponding controls.
Ophthalmoscopy	No drug-related effects.
ECG	No drug-related effects. Standard ECGs were recorded at week -2 and week 39 at 3 hrs post dosing. QTc values were calculated using Bazett's formula.
Hematology	There were slight dose-dependent decreases in red blood cell mass parameters (red blood cell count, hemoglobin and hematocrit) in MD and HD males and females (10% to 25% decreases compared to controls), with a moderate (up to 2-fold) compensatory increase in reticulocytes. A greater effect was observed in males compared to females. The changes correlated with increases in total iron binding capacity and histologic findings in the spleen and bone marrow.
Clinical Chemistry	Triglycerides were markedly increased in MD and HD males and females, but not in a dose-dependent manner (up to 5-fold compared to controls). This finding correlated with increased liver weights and histologic findings in the liver. Slight increases in phosphorus levels were noted in MD and HD males only.
Urinalysis	No drug-related effects.
Gross Pathology	Dark discoloration of the spleen and liver was observed in one HD female, and dark discoloration of the adrenal gland was observed in another HD female and one HD male. An enlarged spleen was observed in one MD female and an enlarged liver was observed in one HD female. Corresponding histopathological findings were observed in the spleen, liver, and adrenal glands of males and females from MD and HD groups.
Organ Weights	Significant increases in relative liver weights were observed in MD and HD males and females (30% and 38% increase compared to controls for HD males and females, respectively). The increased liver weights correlated with histopathological findings.

Parameters	Major findings
Histopathology Adequate battery: Yes	Drug-related findings were observed in the femur (pigmentation) and adrenal glands (decreased lipid droplets) of HD males and females. Findings in the spleen (increased hemosiderin and congestion), bone marrow (increased hemosiderin and increased hematopoiesis), liver (hepatocellular hypertrophy) were observed in MD and HD males and females. The severity of all findings was recorded as "slight". The increased incidence of hepatocyte hypertrophy in the liver correlated with increased liver weights. Increased hemosiderin in the spleen and bone marrow and increased hematopoiesis in bone marrow correlated with hematological changes in red blood cell parameters in MD and HD animals. Pigmentation in the femur of one HD male and two HD females is most likely due to fluoride accumulation in bone, although fluoride levels in bone were not measured, a marked increase in urinary fluoride was observed in MD and HD animals. A similar finding was observed in rats.
[Other evaluations] Biochemical markers of bone turnover	Parameters evaluated: CTx and TRACP 5b markers of bone resorption, and OC, and BAP, markers of bone formation. There was a decrease in BAP for HD males, up to 32% compared to controls.
Iron Metabolism	Increases in total iron binding capacity and unsaturated iron binding capacity were observed for MD and HD males and females compared to controls.
Fluoride in Urine	There was a dose-related increase in urinary fluoride excretion for males and females, with marked increases up to 10-fold for HD males and 11-fold for HD females compared to controls.
Immune Function	There were no significant drug-related findings in any immune function assessments: Immunophenotyping, natural killer cell activity, peripheral blood granulocytes functions, cytokine release.
Bone Densitometry	There were no toxicologically significant changes in DXA whole body, lumbar, or femur parameters or significant changes in pQCT parameters in drug-treated groups compared to controls.

Abbreviations: BAP, bone specific alkaline phosphatase; CTx, C-telopeptides of type I collagen; DXA, dual X-ray absorptiometry; ECG, electrocardiogram; HD: high dose; LD, low dose; MD; mid dose; OC, osteocalcin; pQCT, peripheral quantitative computed tomography; QTc, corrected QT; TRACP 5b, active isoforms 5b of the tartrate-resistance acid phosphatase

Study title/ study number: 13-Week and 26-Week Oral Toxicity Study in Rats/ K12033

- Drug-related deaths (euthanized due to moribund condition or for humane reasons) in one HD male and three HD females. MD and HD females and HD males: adverse bone toxicity (histologic changes in bone structure of decreased trabecular bone or mature lamella bone, decreased bone mineral density (females), and fractures at HD only), adverse teeth toxicity (degeneration of ameloblasts). Decreased serum calcium in MD and HD males and females and decreased serum iron in MD and HD females
- All doses: teeth discoloration and bone pigmentation; no structural changes at the LD
- Increased liver weights for MD and HD males and females, with corresponding hepatocellular hypertrophy at the HD indicative of increased liver metabolizing enzymes
- NOAEL (female) = 30 mg/kg/day; NOAEL (male) = 100 mg/kg/day, which are 41 times and 12 times the MRHD for males and females, respectively based on AUC. Females had higher plasma exposures than males at equivalent doses.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 30, 100, 1000 mg/kg/day once daily for 13 or 26 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Rat/ Sprague Dawley Crl:CD(SD)
Number/Sex/Group:	10 for 13 weeks of dosing 12 for 26 weeks of dosing
Age:	At dosing initiation: 8 weeks
Satellite groups/ unique design:	Toxicokinetics: 4/sex/group
Deviation from study protocol affecting interpretation of results:	No

Table 16: Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	Six HD (2 males, 4 females) died prematurely (one found dead and five were euthanized for humane reasons) during the course of the study. The death of a HD female that was euthanized on day 142 was not determined but is most likely drug-related. The reason for euthanasia of one HD male and two HD females sacrificed on days 153, 134, and 127 was abnormal gait caused by bone fractures of hindlimbs and was drug-related. The two remaining deaths were not drug-related; one HD male (gavage error) and one HD female (euthanized due to accidental injuries of mandibular and hindlimb claw).
Clinical Signs	Tooth discoloration (whiteness of the maxillary incisors) was observed at all dose levels for males and for MD and HD females; the incidence and severity was dose and time-dependent. Tooth discoloration was first observed on day 36 for HD females in 6/22 animals and by day 72 it was observed in all HD females. In HD males, tooth discoloration was first observed on day 50 in all animals. Elongated maxillary incisors were also observed in both sexes at the HD. At the MD, tooth discoloration was first observed on day 75 in both sexes at the same incidence (7/22) and by day 184 8/12 males and females each were affected. Only one LD male was observed with tooth discoloration starting on day 176.
Body Weights	There was a dose-related decrease in mean body weight gain for males during weeks 1-13; approximately 5%, 9%, and 14% decrease for LD, MD, and HD compared to controls, respectively. For females during weeks 1-13, body weight gain was decreased at the HD 26% compared to controls. At the end of the 26 week dosing period, mean body weight gain was only decreased 6% and 3% compared to controls for HD males and females, respectively indicating tolerance to the body weight effects over time. There was no corresponding effect on food consumption.
Ophthalmoscopy	No drug-related effects.

Hematology	Minor decreases in erythroid parameters (decreases in red blood cells, hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin) were observed for HD males and females compared to controls. In addition, activated partial thromboplastin time was prolonged in HD males and an increase in white blood cells was observed for HD females compared to controls.
Clinical Chemistry	Total cholesterol was increased in HD males and MD and HD females, up to 1.4-fold for males and 2.4-fold for females compared to controls. There was a slight increase in total protein, albumin, or globulin in both sexes at MD and HD compared to controls during weeks 13 and 26. Serum potassium was increased for HD females and calcium levels were increased for both sexes at the MD and HD compared to controls. Serum iron was significantly decreased for MD and HD females, 22% and 43% compared to controls. There were no changes in serum markers for bone formation or resorption.
Urinalysis	No drug-related effects.
Gross Pathology	**Text Table 1 Incidence of primary test-article related macroscopic findings**

Sex		Male				Female			
Organ Finding	Dose (mg/kg)	0	30	100	1000	0	30	100	1000
	No. of animals examined[a]	10/12	10/12	10/12	10/10(2)	10/12	10/12	10/12	10/8(4)
Incisor									
Discoloration		0/0	0/1	5/8	10/10(1)	0/0	0/0	2/8	10/8(4)
Liver									
Enlarged		0/0	0/0	0/0	4/2(2)	0/0	0/0	0/0	9/8(0)
Tibia									
Fracture		0/0	0/0	0/0	0/0(1)	0/0	0/0	0/0	0/0(2)
Fibula									
Fracture		0/0	0/0	0/0	0/0(1)	0/0	0/0	0/0	0/0(1)

[a] No. of terminal sacrifice animals in 13-week study / 26-week study
( ): found dead or moribund animals

Source: Applicant's study report K12033 table: NDA 212028

Organ Weights	Liver weights were increased in both sexes in a dose-related manner. The finding correlated with microscopic findings indicative of increased metabolizing enzymes in the liver.

Histopathology

Adequate battery: Yes

Text Table 4 Incidence of Primary Test-article Related Microscopic Findings

Sex		Male				Female			
Organ / Finding	Dose (mg/kg)	0	30	100	1000	0	30	100	1000
No. of animals examined[a]		10/12	10/12	10/12	10/10(2)	10/12	10/12	10/12	10/8(4)
Femur									
Decreased trabecular bone	1+	0/0	0/0	0/0	0/2(0)	0/0	0/0	0/0	3/4(2)
	2+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	3/1(0)
Decreased mature lamellar bone	1+	0/0	0/0	0/0	2/2(0)	0/0	0/0	0/0	7/2(0)
	2+	0/0	0/0	0/0	1/6(1)	0/0	0/0	0/0	2/4(1)
Pigmentation	M	0/0	1/5	1/0	0/0(0)	0/0	0/0	2/1	0/0(0)
	1+	0/0	1/5	4/3	2/4(0)	0/0	0/4	2/3	2/1(0)
	2+	0/0	0/1	3/8	5/5(1)	0/0	0/0	3/7	5/6(4)
	3+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	3/1(0)
Tibia									
Decreased trabecular bone	1+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	3/3(2)
	2+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	3/2(0)
Decreased mature lamellar bone	1+	0/0	0/0	0/0	3/1(0)	0/0	0/0	0/0	6/0(0)
	2+	0/0	0/0	0/0	0/3(0)	0/0	0/0	0/0	1/1(0)
Fracture		0/0	0/0	0/0	0/0(1)	0/0	0/0	0/0	0/0(2)
Pigmentation	M	0/0	0/0	0/1	0/0(0)	0/0	0/0	1/2	0/0(0)

Sex		Male				Female			
Organ / Finding	Dose (mg/kg)	0	30	100	1000	0	30	100	1000
No. of animals examined[a]		10/12	10/12	10/12	10/10(2)	10/12	10/12	10/12	10/8(4)
	1+	0/0	0/0	2/7	5/9(1)	0/0	0/0	6/9	6/5(3)
	2+	0/0	0/0	0/3	4/1(0)	0/0	0/0	0/1	3/3(1)
	3+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	1/0(0)
Sternum									
Pigmentation	1+	0/0	0/0	0/1	0/4(1)	0/0	0/0	0/1	2/3(1)
	2+	0/0	0/0	0/0	0/3(0)	0/0	0/0	0/0	1/5(0)
Fibula									
Fracture		0/0	0/0	0/0	0/0(1)	0/0	0/0	0/0	0/0(1)
Alveolar bone									
Pigmentation	1+	0/0	0/0	1/0	6/2(0)	0/0	0/0	0/0	2/2(0)
	2+	0/0	0/0	0/0	4/7(1)	0/0	0/0	0/0	8/6(3)
	3+	0/0	0/0	0/0	0/1(0)	0/0	0/0	0/0	0/0(1)
Incisor									
Decreased iron contents, ameloblasts	1+	0/0	0/0	0/0	5/6(1)	0/0	0/0	0/1	0/2(0)
	2+	0/0	0/0	0/0	4/3(0)	0/0	0/0	0/0	10/6(4)
Degeneration, ameloblasts	1+	0/0	0/0	0/0	1/3(1)	0/0	0/0	0/0	1/2(0)
	2+	0/0	0/0	0/0	0/1(0)	0/0	0/0	0/0	6/6(3)
Pigmentation, dentin	1+	0/0	0/0	1/1	8/10(1)	0/0	0/0	0/1	5/4(3)
	2+	0/0	0/0	0/0	1/0(0)	0/0	0/0	0/0	5/4(1)
Molar									
Pigmentation, dentin	1+	0/0	0/0	0/0	1/0(0)	0/0	0/0	0/0	3/6(2)
Liver									
Hypertrophy, hepatocytes	1+	0/0	0/0	0/0	2/2(1)	0/0	0/0	0/0	4/4(3)
	2+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	6/4(1)
Thyroids									
Follicular cell hypertrophy	1+	0/0	0/0	0/0	0/0(0)	0/0	0/0	0/0	2/2(0)

[a] No. of terminal sacrifice animals in 13-week study / 26-week study
( ): found dead or moribund animals
GRADE; M: minimal (for pigmentation only), 1+: slight, 2+: moderate, 3+: marked

Source: Applicant's study report K12033 table: NDA 212028

[Other Evaluations] The pigment observed in the bone and teeth stained positive for Berlin blue (iron) and Periodic acid-Schiff (polysaccharides).

Bone Mineral Density Bone mineral density was decreased (as measured by DXA) for HD females at week 13 and for MD and HD females at week 26, up to 17% compared to controls.

Abbreviations: DXA, dual energy X-ray absorptiometry; HD, high dose; LD, low dose; MD, mid dose

General Toxicology; Additional Studies

Single-dose toxicity studies:

Extended single-dose, GLP, toxicity studies with a 2-week recovery period were conducted in rats (study no. S10120) and monkeys (study no. S10118). E2006 was administered by oral gavage in both species at dose levels of 0, 100, 300, and 1000 mg/kg. E2006 was well tolerated in rats up to 1000 mg/kg with increased liver weights in males and females at 300 and 1000 mg/kg, but without corresponding microscopic findings. The NOAEL for rats was 1000 mg/kg. In monkeys, gastro-intestinal-related clinical signs of vomiting and soft feces were observed at 1000 mg/kg and a decrease in serum chloride was also observed at 1000 mg/kg in monkeys. The NOAEL in monkeys was 300 mg/kg due to GI-related clinical signs.

Rat

7-day dose-range-finding toxicity study (study no. S10043), non-GLP

Sprague-Dawley rats (3/sex/group + 3/sex/drug-treated group for TK) were administered E2006 by oral gavage at doses of 0, 100, 300, 1000 mg/kg/day in a vehicle of 0.5w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]) for 7 days. There were no findings in males at any dose level. There was a slight decrease in food consumption for females at 1000 mg/kg/day, but no changes in body weight. Females at 1000 mg/kg/day also had increased liver weights, and increases in total cholesterol, without corresponding macroscopic or microscopic findings. E2006 was well tolerated in males and females at 1000 mg/kg/day for 7 days.

4-week repeat-dose toxicity study (study no. K11004), GLP

Sprague-Dawley rats (10/sex/group + 4/sex/group for TK) were administered E2006 by oral gavage at doses of 0, 30, 100, 1000 mg/kg/day in a vehicle of 0.5w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]) for four weeks. Females at 1000 mg/kg/day had a 23% decrease in body weight gain compared to controls, which correlated with decreases in food consumption. A few high dose females had decreased reticulocyte counts, pre-renal azotemia, bone marrow hypocellularity and thymic lymphoid depletion which were considered secondary to decreased body weight. High dose females also had a 2-fold increase in liver weights which correlated with centrilobular hepatocyte hypertrophy and increases in total protein and cholesterol. Liver sections from 3 control and 3 high dose females were subjected to immunohistochemistry staining with antibodies against cytochrome P450 enzymes 1A2, 3A1, and 3A4 (study no. K12012). Moderate increases in staining were observed for CYP1A2 and marked increases in staining for CYP3A1 and CYP3A4 in liver sections from high dose E2006 rats indicating that E2006 induces hepatic enzyme induction which correlated with hepatocellular hypertrophy. Minimal pigmentation in the femur was observed in 1/10 and 5/10 high dose males and females, respectively without any other corresponding microscopic changes in the femur. The NOAEL was the high dose of 1000 mg/kg/day in males and the mid dose of 100 mg/kg/day in females due to decreased body weight gain. Plasma exposure (AUC) was higher in females than males at equivalent doses.

Rat bone toxicity mechanistic follow-up studies:

A GLP mechanistic study entitled "E2006: A 14-Week oral toxicity study in female rat with 12-week recovery period" (study no. 6700122) was undertaken to assess the potential mechanism of the skeletal and dental changes produced by E2006 in the 13-/26-week oral repeat dose study (study no. K12033). Female rats (46/group) were administered vehicle (0.5 w/v% methylcellulose solution mixed in a 1:4 [v/v] ratio) or 1000/800 mg/kg/day E2006 by oral gavage for 9 or 14 consecutive weeks. Male rats were not tested because exposure and toxicity were more pronounced in female rats at the equivalent doses. Due to marked body weight loss during the first 2 weeks of the study, animals were given a 7-day dosing holiday starting on day 15 and dosing resumed on day 22 at 800 mg/kg/day. Animals with marked body weight loss were sacrificed in week 9 (16 animals, with the same number of control animals), the remaining animals continued to receive treatment until week 14 at which point 15 animals/group were necropsied and the remaining 15 animals/group were necropsied at week 26 following a 12-week recovery period. The following parameters were evaluated: mortality, clinical signs, body weights, food consumption, clinical chemistry, hematology, iron metabolism, fluoride in urine/serum/bone (humerus), biochemical markers of bone turnover, hormones (parathyroid hormone, ACTH and 1, 25-dihydroxyvitamin D), toxicokinetics, organ weights, macroscopic and microscopic pathology, bone densitometry (dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT)), micro-computed tomography (micro-CT), biomechanical testing of bone (including load and strength), and ash testing for tissue mineralization.

Similar to the previous studies, animals had a loss of body weight which correlated with a decrease in food consumption. Animals displayed discoloration of the incisors starting at week 5. Macroscopic findings at weeks 9 and 14 included discoloration of teeth in all drug-treated animals; findings at week 26 (recovery group) included tibia bone fracture in 3 of 15 drug-treated animals and teeth discoloration in 4 of 15 drug-treated animals. Microscopic findings were observed in the tibia, femur, and incisor of drug-treated animals at week 14, with significantly less findings at the recovery necropsy during week 26. Analysis revealed an increase in urinary fluoride excretion that was 28-53-fold higher than control animals between study weeks 9-14. Additionally, there was an increase in serum fluoride in 6 of 14 drug-treated animals and a high concentration of fluoride in the bone of treated animals (14 fold higher than control). Extensive characterization of the bone demonstrated lower bone mineral density and bone mineral content with associated decreases in bone strength. Drug-treated animals also had a dysregulation of bone resorption and formation markers, decreased ACTH and serum iron levels and lower absolute and relative adrenal glands weights. Most of the changes in the study were reversible upon drug cessation. The study results suggest that after repeated high doses of E2006 (≥800 mg/kg/day), there is an increase of fluoride in urine, serum, and bone that negatively affects the teeth and bone.

A toxicity study was conducted to investigate if the bone and teeth toxicity observed in rats after repeat dosing of E2006 could be related to fluoride accumulation as a result of fluoride being released during the metabolism of E2006. A study entitled "sodium fluoride: a 26-week

oral toxicity study in female rats" (study no. K13084) evaluated the effects of repeat oral dosing of sodium fluoride (0, 10, 25, or 50 mg/kg/day) to female Sprague-Dawley rats (20/group) for 15 or 26 consecutive weeks. Rats developed whitish bands on the incisors and changes in microscopic content of the incisors. Bone changes included increased bone fractures, decreased bone density, decreased bone strength, decrease in ash content, and increased bone fluoride concentrations. In addition, animals had changes in blood chemistry and iron metabolism. The changes in this study with sodium fluoride are similar in nature to changes seen in rats treated with E2006.

A study entitled "A 4-week fluoride measurement study in female rats" (study no. K14010) was conducted to measure fluoride concentrations in urine, serum, and bone of female rats orally treated with E2006 (0, 30, 100, or 1000 mg/kg/day) for 4 weeks because fluoride measurements were not conducted in a previous 4-week toxicity study (study no. K11004). This study demonstrates that, although bone and teeth changes are not yet apparent at 4 weeks (except for pigmentation in the femur at the highest dose), administration of E2006 at doses above 100 mg/kg/day leads to increases in urinary excretion of fluoride after just one dose and bone accumulation of fluoride by 28 days.

Monkey

A 4-week oral toxicity study in monkeys (study no. SBL038-055), GLP

Cynomolgus monkeys (4/sex/group) were administered E2006 by oral gavage at doses of 0, 30, 100, 1000 mg/kg/day in a vehicle of 0.5w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]) for four weeks. Gastrointestinal (GI) related clinical signs consisting of vomiting and salivation were observed in males and females at doses ≥100 mg/kg/day which correlated with slight decreases in food consumption for females at ≥100 mg/kg/day and males at 1000 mg/kg/day. Clinical signs related to the pharmacology of the drug including sedation, sitting position, incomplete eyelid opening, and somnolence were observed in one to two high dose males. Dose-related effects on red blood cell parameters were observed in males and females including decreases in red blood cell counts, hemoglobin, and hematocrit compared to controls and predose levels. A compensatory dose-related increase in reticulocytes was observed in males and females. "In only one male at 1000 mg/kg, there was a complex clinical syndrome of undetermined cause and relationship to the test article with changes including renal glomerulonephropathy, pulmonary thrombosis, edema in subcutis, and inflammation in the large intestine with correlated clinical pathology changes." The NOAEL was the low dose of 30 mg/kg/day for both males and females due to adverse GI-related clinical signs, which produced plasma AUC levels of E2006 on day 28 of 27335 ng.hr/ml and 18192 ng.hr/ml in males and females, respectively.

A 13-week oral toxicity study in monkeys (study no. SBL038-067), GLP

Cynomolgus monkeys (4/sex/group) were administered E2006 by oral gavage at doses of 0, 20, 100, 1000 mg/kg/day in a vehicle of 0.5w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]) for four weeks. One male at 100 mg/kg/day died on day 41 due to an intubation error. Vomiting and salivation were observed in all animals at 100 and 1000 mg/kg/day.

Sedation and sitting position were observed in one male and one female at 1000 mg/kg/day approximately 4 hours after dosing on day two. Triglycerides were increased in males and females at 1000 mg/kg/day compared to controls. Decreases in erythrocyte parameters (red blood cell counts, hemoglobin, and hematocrit) were observed in males and females at ≥100 mg/kg/day with increased severity in males compared to females. An adaptive increase in reticulocytes was observed in these animals. One male at 1000 mg/kg/day had severe anemia (>80% decrease in red blood cell counts, hemoglobin, and hematocrit compared to controls) and an 8-fold increase in eosinophils. This animal was later confirmed to have malaria as a result of infection with the parasite Plasmodium spp. This animal also had macro- and microscopic findings in the spleen, liver, and bone marrow. Bone marrow smear analysis revealed parasite-containing erythrocytes across all dose groups for males and in one high dose female, which was dose-related for males. The parasitemia correlated with microscopic findings in the spleen and bone marrow in drug-treated animals as well as in the spleen of one control male, suggesting that animals in this cohort were sub-clinically infected by Plasmodium spp. Due to the dose-related recrudescence of latent malaria observed in this study a follow-up non-GLP mechanistic study entitled "E2006: An investigative study to evaluate the effect on in vitro culture of Plasmodium falciparum with human erythrocytes" (study no. W-20140891) was conducted to identify the mechanism of the recrudescence. E2006 did not accelerate parasite growth in vitro at concentrations up to 100 µg/mL. All animals were negative for Plasmodium in the 39-week repeat-dose toxicity study and no animals presented with severe anemia in that study.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ study number: E2006: Reverse mutation assay in bacteria/S11002

Key Study Findings:

- E2006 was negative for mutagenicity in bacterial cells in a valid Ames test. GLP compliance: Yes
- GLP compliance: Yes
- Test system: Salmonella typhimurium strains TA100, TA1535, TA98, and TA1537, E. Coli strain WP2 uvrA (pKM101); doses ≤5000 µg/plate in DMSO; +/- S9
- Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ study number: E2006: Mouse Lymphoma tk Assay/K11008

Key Study Findings:

- E2006 did not increase the mutation frequency or the percent of small and large colonies at any concentration.
- E2006 was not mutagenic or clastogenic in the mouse lymphoma thymidine kinase assay. GLP compliance: Yes
- GLP compliance: Yes

- Test system: Mouse lymphoma L5178Y tk+/- cells; doses ≤200 µg/ml for 3-hour incubation +/- S9 and ≤80 µg/ml for 24-hour incubation -S9
- Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ study number: E2006: Micronucleus Assay in Rats after Oral Administration/K11011

Key Study Findings:

- There was no statistically significant increase in micronuclei; E2006 was not clastogenic in male rats at doses up to 2000 mg/kg for two days.
- Toxicokinetics was not conducted in the study. GLP compliance: Yes
- GLP compliance: Yes
- Test system: Male Sprague-Dawley rats; bone marrow micronuclei; one or two doses of E2006 500, 1000, or 2000 mg/kg by oral gavage
- Study is valid: Yes

5.5.3. Carcinogenicity

Study title/ study number: E2006: An Oral Carcinogenicity Study in Rats / K13092

Sprague Dawley rats (60/sex/group) were administered lemborexant by oral gavage in a vehicle of 0.5 w/v% methylcellulose for 104 consecutive weeks. Doses of 30, 100, and 300 mg/kg/day were used for males and 10, 30, and 100 mg/kg/day for females. There was no statistically significant effect on survival. There was a greater than 10% decrease in absolute body weight for males at 300 mg/kg/day compared to controls, without an effect on food consumption. The study was negative, as there were no statistically significant drug-related neoplastic findings in either males or females. Exposure (AUC) at 300 mg/kg/day in males and 100 mg/kg/day in females, is >82 times the exposure at steady state at the maximum recommended human dose (MRHD) of 10 mg.

There were drug-related findings in males and females consistent with fluorosis including clinical signs, macroscopic, and non-neoplastic microscopic findings in teeth and bone. These findings were similar to those observed in rats from the 13/26-week toxicity study and are considered related to fluorosis. The incidence and severity of the findings at doses used in the 2-year study were increased compared to similar doses in the 13/26-week repeat dose toxicity study indicating the effect is dose- and duration-dependent (see appendix for details).

Study title/ study number: E2006: A 26-Week Oral Carcinogenicity Study in CB6F1-Tg rasH2 Mice / K15016

Tg.rasH2 mice (25/sex/group) were administered lemborexant by oral gavage in a vehicle of 0.5 w/v% methylcellulose for 26 consecutive weeks. Doses of 50, 150, and 500 mg/kg/day were used for males and females. There was no statistically significant effect on survival. There was a statistically significant increase in the incidence of hemangiosarcoma in the spleen and combined tumors of hemangiosarcoma and hemangiomas in the whole body for drug-treated

male mice; however, the findings were positive only in the trend test compared to vehicle control, but not in pairwise tests. The incidence rate for hemangiosarcoma in the spleen and hemangiosarcoma and hemangiomas in the whole body for males was outside the laboratory historical control range, although there was a limited number of animals in the dataset. These tumors were found at a higher background incidence rate in the published literature for male Tg.rasH2 mice. There was no statistically significant increase in any tumor types for females. The study was therefore negative, as there were no statistically significant drug-related neoplastic findings in either males or females.

The Executive Carcinogenicity Assessment Committee (ECAC) agreed that the rat and mouse carcinogenicity studies were adequate, noting prior approval of the protocols. The ECAC concurred with the Applicant and the FDA statistical analyses, that there were no drug-related neoplasms in the 2-year rat study and 6-month mouse study in either males or females.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ study number: E2006: An Oral Fertility and Early Embryonic Development Study in Male Rats/ K13078

Key Study Findings

- No effects on any fertility parameters.
- The NOAEL for male fertility is 1000 mg/kg/day which is approximately 138 times the maximum recommended human dose (MRHD) based on AUC. Toxicokinetics was not measured in this study; plasma AUC values at 1000 mg/kg/day taken from the rat 13/26-week study no. K12033.

Conducting laboratory and location	(b) (4)
GLP compliance: Yes	

Methods

Dose and frequency of dosing:	0, 30, 100, 1000 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Rat/Sprague-Dawley (males) from (b) (4)
Number/Sex/Group:	20
Satellite groups:	NA

Study design:	Animals were dosed once daily for 28 days prior to mating, and throughout the mating period (for a maximum of 13 days). Each male was cohabited with one untreated female for a maximum of 14 days. After the mating period all surviving males were euthanized and subject to necropsy. All females were euthanized on Gestation Day (GD) 14.
Deviation from study protocol affecting interpretation of results:	No

Table 17: Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	No drug-related effects.
Body Weights	No drug-related effects.
Necropsy findings	No drug-related effects.
Mating/Fertility index Uterine parameters for females	No drug-related effects.

Fertility and Early Embryonic Development

Study title/ study number: E2006: An Oral Fertility and Early Embryonic Development Study in Female Rats/ K13063

Key Study Findings

- There was a significant decrease in body weight and food consumption at 1000 mg/kg/day during the premating and gestation periods.
- There was an increase in the number of animals with irregular estrous cycles at doses ≥100 mg/kg/day, which may be related to the pharmacology of the drug and its effects on hormone regulation, specifically luteinizing hormone (LH); however, LH levels were not measured in this, or any other, study.
- A significant decrease in pregnancy rates were observed at doses 100 ≥ mg/kg/day compared to controls.
- A significant decrease in the number of corpora lutea, implantations, and live embryos occurred at 1000 mg/kg/day.
- The NOAEL is 30 mg/kg/day for effects on female fertility, which is approximately 29 times and 12 times the MRHD based on mg/m^2 and AUC*, respectively. *Toxicokinetics was not measured in this study, plasma AUC values at 30 mg/kg/day taken from the rat 13/26-week study no. K12033.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 30, 100, 1000 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Rat/Sprague-Dawley (females) from (b) (4)
Number/Sex/Group:	20
Satellite groups:	NA
Study design:	Animals were dosed once daily starting 14 days prior to mating, throughout the mating period for a maximum of 13 days, and up to GD6. All females which had copulated were euthanized on GD14 and subjected to a cesarean section.
Deviation from study protocol affecting interpretation of results:	No

Table 18: Observations and Results

Parameters	Major findings
Mortality	Four non-drug related deaths occurred in HD animals during the study. Two animals were found dead after dosing on GD7, cause of death was gavage errors. These two animals were replaced with two additional animals. Another HD animal was found dead before dosing on GD4 and the death was considered a gavage error due to histopathologic changes of neutrophil infiltration in the tracheal mucosa. One HD animal was sacrificed moribund on GD10. No definitive cause of death was determined. This animal had staining of the genital region, staining of nose, few or no feces, decreased activity, or abnormal respiratory sounds starting on GD7. The Applicant suggests the death could be gavage error due to histologic changes of distended esophagus that contained food and this reviewer agrees.
Clinical Signs	Clinical signs in surviving animals included abnormal respiratory sounds and staining of the nose in one HD animal. Similar signs were observed in animals that were found dead or sacrificed moribund and may be related to gavage accidents.
Body Weights	Premating: There was a statistically significant decrease in body weight for HD animals on premating days 10 (6%), and 13 (9%), compared to control. There was an overall body weight loss of 8 g for HD animals from premating day 1 to 13, compared to overall body weight gain of 17 to 21 g for all other groups. The body weight loss correlated with a statistically significant decrease in food consumption compared to controls. Gestation period: Body weight values were statistically significantly decreased for HD animals during GD0 to GD14, with an overall body weight gain decrease of 76% compared to control between GD0 to GD6. The body weight effects correlated with a statistically significant decrease in food consumption from GD1 to 4 compared to control.
Necropsy findings	No drug-related findings.
[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]	There was a dose-dependent decrease in pregnancy rates: 85%, 85%, 74%, and 58% in control, LD, MD, and HD groups, respectively (pregnant females: 17, 17, 14, and 11 respectively). There was also a statistically significant decrease in the mean number of corpora lutea, implantations, and live embryos for HD animals, 17%, 17%, and 21% decrease compared to control, respectively. Although there was no drug-related effect on estrous cycle lengths, there was an increase in the number of animals with irregular estrous cycles at the MD and HD (1, 1, 4, and 7 animals in control, LD, MD, and HD, respectively). There was no drug-related effect on average length of the mating period or the number of animals that had evidence of copulation.

Abbreviations: GD, gestational day; HD: high dose; LD, low dose; MD, mid dose

Embryo-Fetal Development

Study title/ study number: E2006: An Oral Embryo-Fetal Development Study in Rabbits/ K12011

Key Study Findings

- Maternal toxicity was observed at 100 mg/kg/day which consisted of decreased body weight that correlated with decreased food consumption.
- Fetal toxicities observed at 100 mg/kg/day included the skeletal variation of the presence of cervical ribs and the visceral variation of supernumerary lung lobes.
- The NOAEL is 30 mg/kg/day for maternal toxicity and embryofetal development, which is 23 times the MRHD, based on AUC.

Conducting laboratory and location:	(b) (4)
GLP compliance: Yes	

Methods

Dose and frequency of dosing:	0, 10, 30, 100 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Rabbit/female New Zealand White from (b) (4)
Number/Sex/Group:	20
Satellite groups:	NA
Study design:	Pregnant rabbits were dosed for 14 consecutive days, from GD7 to 20, and all surviving animals were euthanized, and cesarean sections were performed on GD29. Live fetuses were weighed, and morphologic exams were conducted. Blood samples were collected from 5 animals/group on GD20 for toxicokinetic analysis.
Deviation from study protocol affecting interpretation of results:	No

Table 19: Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	One HD animal aborted on GD23. This animal had a marked decrease in food consumption and body weight on all dosing days prior to aborting however, a hairball was found in this animal upon necropsy that could have contributed to decreased food consumption, weight loss and consequently abortion. Partially closed eyes indicative of sedation were observed in one to four animals in all drug-treated groups during the dosing period and is likely related to the pharmacology of the drug; this finding was absent when dosing was discontinued. Few feces that correlated with decreased food consumption was observed in several HD animals.
Body Weights	Mean body weight values for HD animals were slightly decreased, but not statistically significant, compared to control during the entire dosing period. However, body weight values at this dose were comparable to controls after drug cessation from GD23 to 29. There was an overall non-statistically significant decrease in body weight gain for HD animals during dosing period of 87% compared to control, which correlated with a 20% decrease in food consumption compared to control from GD7 to 9.

Parameters	Major findings
Necropsy findings Cesarean Section Data	There were no statistically significant, or drug-related, effects on any parameters, including number of live fetuses, implantation sites, pre- and post-implantation loss, fetal weighs, and fetal sex ratios.
Necropsy findings Offspring (Malformations, variations, etc.)	There was a statistically significant increase in the number of fetuses with cervical ribs (a skeletal variation of an extra rib located off the cervical vertebrae) for HD animals compared to control, 13 fetuses (9.3%) compared to 1 fetus (0.7%), respectively. The fetal incidence rate of cervical ribs observed in fetuses at 100 mg/kg/day was higher than the incidence rates reported in historical control data from both the conducting laboratory and data reported in published literature. There was a dose-related increase in the number of fetuses with the visceral variation of abnormal lung lobation: 5 (2.8%), 7 (3.8%), 8 (4.2%), and 10 (7.0%) for control, LD, MD, and HD, respectively. The Applicant did not consider the general finding of abnormal lung lobation to be drug-related because the fetal incidence at 100 mg/kg/day was within the historical control range of up to 8.65% (per study). However, the additional information provided in SDN 18, revealed that the finding was outside the laboratory historical control range of up to 2.8%. More importantly, when the finding was separated into findings of incomplete lobation and supernumerary lobes, the increased incidence of supernumerary lobes was dose-related and was higher than the incidence rates reported in historical control data from the conducting laboratory. Because the historical control data from published literature did not separate the findings into incomplete lobation and supernumerary lobes and the incidence rates of supernumerary ribs in fetuses at 10 and 30 mg/kg/day are close to the historical control rates for the laboratory (up to 2.8%), the findings at 10 and 30 mg/kg/day are not considered drug-related. However, the increased incidence of supernumerary lung lobes in fetuses at 100 mg/kg/day is considered a drug-related finding. There were no drug-related external or skeletal malformations, or changes in ossification patterns.

Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose; SDN, supporting document number

Table 20: Incidence of Abnormal Lung Lobation in Rabbit Fetuses Compared With Historical Controls

	Study K12011				Historical Control Data	
	Control (0 mg/kg)	10 mg/kg	30 mg/kg	100 mg/kg	(b) (4)	(b) (4) Laboratories[b]
No. of dams	19	19	20	18	193	145–686[c]
No. of fetuses examined	152	157	141	140	1436	1076–5580[d]
	Number of Affected Fetuses (Mean %)				Mean % [min – max]	
Abnormal lung lobation	5 (2.8)	7 (3.8)	8 (4.2)	10 (7.0)	0.5 [0.0 – 2.8[f]]	0.02 – 2.44[e] [0.00 – 8.65[f]]
Abnormal lobation	4 (2.2)	2 (1.2)	2 (1.1)	3 (2.3)	0.4 [0.0 – 2.5[f]]	ND
Supernumerary lobes	1 (0.6)	5 (2.6)	6 (3.1)	7 (4.7)	0.1 [0.0 – 0.6[f]]	ND

Mean % is the litter incidence defined as: (sum of affected fetuses [%] per litter)/(total no. of litters).
EFD = embryo-fetal development, ND = not determined.
a: The historical control data from (b) (4) includes 12 rabbit EFD studies with fetal visceral and skeletal examinations. Source: Noritake, 2016.
b: Historical control data for rabbit prenatal developmental toxicity studies performed between 2001-2010 by (b) (4) laboratories (including (b) (4) contributing data to Ema, et al. (2012).
c: Range of the number of dams per laboratory.
d: Range of the number of fetuses per laboratory.
e: Range of the mean % of fetuses with abnormal lung lobation per laboratory.
f: Range of the mean % of fetuses with abnormal lung lobation per study.
Source: Applicant's table: NDA 212028, SDN 18

Embryo-Fetal Development

Study title/ study number: E2006: An Oral Embryo-Fetal Development Study in Rats/ K12010

Key Study Findings

- 600 mg/kg/day (HD):
  - Significant decrease in body weight and food consumption
  - Slight, increase in postimplantation loss and decrease in mean fetal weights
  - Increased incidence of external malformations: cleft palate and omphalocele
  - Increased incidence of visceral malformation of membranous ventricular septum defect
  - Increase in skeletal variations: 14th cervical rib, and increase in incomplete ossification
- One fetus each at 60 and 200 mg/kg/day had membranous ventricular septum defect with no findings in controls or the laboratory historical control dataset (at the time). Additional study and background incidence from published literature showed this incidence to be within historical/lab control background.
- The NOAEL is 200 mg/kg/day for maternal toxicity and embryofetal development findings, which is 143 times the MRHD, based on AUC.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 60, 200, 600 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution/1 M hydrochloric acid [4:1, v/v]
Species/Strain:	Rat/Sprague-Dawley, female, from (b) (4)
Number/Sex/Group:	20 for control, LD, and MD; 22 for HD
Satellite groups:	5-6/group for toxicokinetic analysis on GD17
Study design:	Pregnant rats were lemborexant dosed once daily from Gestation Day (GD) 6 to GD17. Animals were euthanized on GD20 and subjected to a cesarean section and uterine and fetal examinations.
Deviation from study protocol affecting interpretation of results:	No

Table 21: Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	Decreased activity, staining of the anogenital region, and few feces were observed in one or two HD animals between GD14 and GD19, compared to no clinical signs observed in any other group.
Body Weights	There was a statistically significant decrease in mean body weight for HD animals compared to control starting on GD11 and continuing until the end of the study on GD20; overall body weight gain was decreased 63% compared to control between GD6 and 18. After cessation of dosing, body weight gain for HD animals was statistically significantly increased 41% compared to control between GD18 and 20 indicating a full reversibility of the effect. There was a slight, transient, non-statistically significant decrease in body weight for MD animals between GD7 and 9. The effects on body weight correlated with effects on food consumption
Necropsy findings	No drug-related findings.
Necropsy findings Cesarean Section Data	At the HD, there was a non-statistically significant increase in postimplantation loss (5.8% compared to 4.0% for control), including an increased number of dead fetuses (0.8% compared to 0.0% for control) and early resorptions (5.0% compared to 3.4% for control). Mean fetal body weights were slightly decreased from HD animals, 7% compared to control.
Necropsy findings Offspring	External anomalies (malformations): Two fetuses from two HD litters had omphalocele and one of those fetuses also had cleft palate. There were no incidences of cleft palate or omphalocele in any other group including control or in the laboratory historical control dataset at the time the study was conducted (1067 control fetuses (163 litters) from 9 studies conducted between 2002 and 2010). Visceral anomalies (malformations): Membranous ventricular septum defect which was observed in 5 fetuses from four HD litters (3.6% fetal incidence and 18.2% litter incidence), compared to no findings in control. One fetus each from the LD and MD groups also had this finding (0.8% and 1.0% fetal incidence, respectively). Membranous ventricular septum defect was not observed in the laboratory historical control dataset from studies conducted between 2002 and 2010. However, the Applicant conducted two additional rat embryofetal development studies to investigate this finding (studies K12080 and 20060758), a new study to investigate the background effect in Sprague-Dawley rat fetuses in the same testing facility (study no. K13048) and provided data from published literature on the background incidence of this finding in Sprague-Dawley rats. Fetal and litter incidence rates of 0.6% and 5.8%, respectively were determined from the study no. K13048, and published literature reported fetal incidence rates between 0% and 3%. Therefore, the finding of membranous ventricular septum defect in one fetus each from the LD and MD groups are considered background and not drug-related. Skeletal variations: There was a statistically significant increase in the number of skeletal variations at the HD compared to control; including 14th cervical rib (57% fetal incidence compared to 13% in the control), and a non-statistically significant increases in incomplete ossification of the cervical arch (16% fetal incidence compared to 0.8% in the control) and thoracic centrum (10% fetal incidence compared to 0.7% in the control).

Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose

Embryo-Fetal Development

Study title/ study number: An Oral Embryo-Fetal Development Study in Rats (Additional Study)/ K12080

An additional GLP rat embryofetal development study was conducted at the same laboratory and using a similar study design as the first study, except only external and visceral examinations were conducted on fetuses; no skeletal examinations were conducted. Doses used in the additional study were 0, 20, 60, and 200 mg/kg/day. Toxicokinetics was conducted for the vehicle and 20 mg/kg/day groups only because this dose was not included in the previous study. There was a slight, transient, decrease in body weight at the HD between GD7 and 11, 2.6% compared to control, which correlated with a transient decrease in food consumption. Similar to the first rat embryofetal development study (K12010), membranous ventricular septum defect was observed in a few fetuses from drug-treated dams (one fetus at the LD, and two fetuses from two litters at the mid dose, a fetal incidence rate of 0.4% and 0.7%, respectively compared to none in control fetuses. However, in the current study, the effect was not dose-related, as there were no findings at the HD.

Reviewer Comments: *AUC values at 20 mg/kg/day in this study (2845 ng.h/ml) are approximately 9 times lower than AUC values measured at the 60 mg/kg/day in the previous study, with only a 3-fold decrease in dose; C_{max} is dose proportional between the two studies. Therefore, it is possible the low incidence of the finding of membranous ventricular septum defect in this study could be related to lower AUC, although plasma exposure was not measured at 60 and 200 mg/kg/day for comparison.*

Study title/ study number: E2006: An Oral Study in Pregnant Rats for Reversibility of Fetal Membranous Ventricular Septal Defect (mVSD)/ 20060758

A GLP follow-up embryofetal development study was conducted in Sprague-Dawley rats, using a similar study design as the previous rat studies, to investigate reversibility of fetal membranous ventricular septal defect (mVSD). Doses of lemborexant used in the current study were: 20, 60, 200, and 600 mg/kg/day (20 rats/group); another group was dosed with trimethadone as the positive control.

There was a statistically significant decrease in mean fetal body weights at 600 mg/kg/day compared to controls. There were no external malformations in fetuses from any E2006-treated dams. There were no findings of membranous ventricular septum defect (mVSD) in fetuses from any E2006-treated dams or controls, even though the same doses of E2006 used in the current study produced mVSD in two previous rat embryofetal development studies. Cardiovascular abnormalities were observed in 44 fetuses (46%) from 8 litters (100%) in the positive control dose group (trimethadione), including interventricular septal defects (muscular and membranous).

Reviewer Comments: *Major differences between the follow-up study (study no.* 20060758) and previous rat embryofetal development studies included different test facilities and source of animals for the follow-up study (b) (4) and a different lot of drug substance with a higher purity profile was used in the follow-up study. These differences may have contributed to the lack of findings of membranous ventricular septal defect in the follow-up study as compared to the previous rat embryofetal development studies.

Background Incidence Rate Data for Membranous Ventricular Septum Defect in Sprague-Dawley Rats:
The Applicant provided background data for membranous septum defect in Sprague-Dawley rat fetuses from a testing facility generated study, and published literature. An embryo-fetal development study in Sprague-Dawley rats (study no. K13048) was conducted to collect background data in Sprague-Dawley GD20 rat fetuses from the (b) (4) testing facility; the study was initiated June 7, 2013. 69 female Sprague-Dawley rats were administered 0.5% methylcellulose by oral gavage from GD6 to 17 and euthanized on GD20. 444 fetuses from 69 litters were examined for visceral findings. Results: membranous ventricular septal defect was observed in 5 fetuses from 4 litters (fetal incidence: 0.6%, litter incidence: 5.8%).

[13] (Teratology) reported an incidence rate for membranous ventricular septal defects 13/550 fetuses (2%) from 9/40 litters on day 21 (postcoitus) Sprague-Dawley rat fetuses.

[14] (b) (4) reported average fetal incidence rates for membranous ventricular septal defect in GD20 Sprague-Dawley rat fetuses of 0% to 3% across numerous laboratories in Japan from studies conducted between 1986 and 1993.

Prenatal and Postnatal Development
Study title/ study number: E2006: An Oral Toxicity Study of Effects on Pre- and Postnatal Development, Including Maternal Function in Rats/ 20060760
Key Study Findings

- E2006 administration at 300 mg/kg/ (HD) resulted in a significant decrease in body weight gain during gestation and lactation periods, which corresponded with decreases in food consumption.
- F1 pup body weights from the HD group were significantly decreased up to postnatal day 36.
- F1 pup femur lengths were decreased in the HD group on PND 21.
- There was a significant decrease in the acoustic startle response in F1 male and female pups in the HD group on PND 23.
- There were slight decreases in bone biomarkers, total iron binding capacity and unsaturated iron binding capacity, on PNDs 21 and 70 for F1 pups from the HD group. An increase in bone fluoride levels on PND 21 were observed for F1 pups from the HD group; without any corresponding histopathologic findings in the femurs.
- The maternal and F1 NOAEL is 100 mg/kg/day, which is 93 times the MRHD, based on AUC.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 30, 100, 300 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution in 1 M hydrochloric acid [mixed 4:1, v/v]
Species/Strain:	Rat/Sprague-Dawley from (b) (4)
Number/Sex/Group:	22
Satellite groups:	Toxicokinetic satellite groups: 3-4/group were dosed until GD17
Study design:	Animals were dosed once daily from GD6 to lactation day (LD) 20. F0 females were allowed to deliver naturally and were monitored to weaning (LD21), F1 offspring (2/sex/litter) were assigned to one of two subgroups (A or B) for continued evaluation for developmental, behavioral, and reproductive effects (Subset A) or bone evaluations (Subset B).
Deviation from study protocol affecting interpretation of results:	No

Table 22: Observations and Results

Generation	Major Findings
0 Dams	Mean body weights and body weight gain for HD animals were statistically significantly decreased during most of the gestation period, 15% decrease in body weight gain from GD6 to 20 compared to control, which correlated with a 14% decrease in food consumption compared to control. Mean body weights remained statistically significantly decreased compared to control through most of the lactation period (LD4 to LD14), which correlated with a 16% decrease in food consumption compared to control. All rats were pregnant and delivered litters; there were no drug-related effects on any uterine parameters, number of live or stillborn pups.
F1 Generation	Body weight: HD: There was a statistically significant decrease in male and female pup mean body weights (17% decrease compared to control) during the pre-weaning post-natal period, PND 1 to 21. Post-weaning, mean pup body weights and body weight gains were still statistically significantly decreased until PND 36, up to 17% compared to control. After PND 36, mean pup body weight gains were comparable to controls. There was no corresponding decrease in food consumption. Neurological assessment: There was a statistically significant decrease in the acoustic startle response on PND 23 for male and female pups from the HD group compared to control, as measured by a decrease in the average response amplitude and the maximum response amplitude for the pooled five trial block sets. There was also a statistically significant increase in the latency to the maximum response amplitude for HD males for all the block trial sets and for HD females for the first block of trials. Reproduction: There were no drug-related findings. Bone examination: (femur lengths: PNDs 21 culled pups and PND 70 [Subset B]), bone biomarkers (PND 21 culled pups and PND 70), bone fluoride measurement (PND 21 culled pups and PND 70), and femur histology (PND 21 culled pups and PND 70): PND 21 femur lengths of male and female HD pups were statistically significantly decreased, 3% and 5% compared to control, respectively. There were no drug-related effects on femur lengths in the PND 70 subset F1 pups. There were no drug-related effects on the bone biomarkers: calcium, inorganic phosphorus, or iron. The bone biomarker mean total iron binding capacity, (TIBC) was statistically significantly decreased for male HD pups on PND 21 and 70 compared to control. Unsaturated iron binding capacity (UIBC) was statistically significantly decreased for female MD and HD pups on PND 70 compared to control. Fluoride was detected in the bone (tibia) of F1 male and female HD pups on PND 21, compared to no measurable fluoride levels in bone from the control groups. Very low level of fluoride was measurable in a few pups from the MD. On PND 70, bone fluoride levels in HD pups were only slightly higher than levels in the control groups. The slight decrease in TIBC and increased bone fluoride levels are not considered to be toxicologically relevant because there were no correlating histopathologic findings in the femurs of PND 21 or 70 F1 pups.
F2 Generation	Not evaluated

Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose; PND, postnatal day; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity

5.5.5. Other Toxicology Studies

Phototoxicity

Two in vitro phototoxicity assays were conducted with lemborexant; an exploratory non-GLP photoxicity test in mouse Balb/c 3T3 cells (study T14019) and a GLP photoxicity test in Balb/c 3T3 cells (study T17022). The studies were adequately conducted and valid. No precipitation of lemborexant occurred and no cytotoxicity was observed up to the highest concentration tested, 100 µg/ml, with or without irradiation. Lemborexant was not phototoxic under the conditions of these in vitro assays.

Impurities

Impurity (b) (4)**:** The Applicant proposed a specification limit of ≤ (b) (4)% for impurity (b) (4), which is above the quantification limit based on ICH Q3A. The limit of ≤ (b) (4)% is based on a level of (b) (4)% of impurity (b) (4) in the drug substance batch of lemborexant used in animal toxicology studies (13/26-week toxicity study in rats, 13-week toxicity study in monkeys, and embryofetal development studies in rats and rabbits), and a negative quantitative structure activity relationship (Q)SAR assessment using in silico software DEREK Nexus and CASE Ultra. Impurity (b) (4) was present at a level of (b) (4)% in the drug substance batch of lemborexant used in the genetic toxicity studies, in vitro mouse lymphoma study, and in vivo rat micronucleus assay. Impurity (b) (4) is adequately qualified in nonclinical studies up to a specification limit of ≤ (b) (4)%.

An assessment of potential genotoxicity was conducted for starting materials, intermediates, and impurities of lemborexant. Ten of those compounds were found to be positive for mutagenicity by (Q)SAR in silico software programs DEREK Nexus and CASE Ultra, and were subsequently tested in in vitro Ames assays. Five of the Ames tests were positive and therefore those impurities are considered genotoxic ((b) (4) , and are controlled according to ICH M7.

6. Clinical Pharmacology

6.1. Executive Summary

The clinical development program includes 16 phase 1 clinical pharmacology trials (i.e., single- and multiple-ascending dose, food effect, mass balance, drug interaction, renal and hepatic impairment, abuse potential, TQT, and driving performance studies), two phase trials, and two phase 3 efficacy/safety trials. The Applicant is relying on two positive phase 3 trials to support effectiveness and safety for lemborexant. In addition, the submission contains 17 *in vitro* studies evaluating distribution, metabolism, protein binding, metabolic/transporter-based drug interactions, etc. Population pharmacokinetic analysis and physiologically based pharmacokinetic (PBPK) analysis are also included in the submission.

Key issues addressed in this review are:

1. Appropriateness of the proposed dosing regimen in the general population.
2. Appropriateness of the proposed dosing regimen in specific patient populations (i.e., hepatic impairment).
3. Appropriateness of the proposed dosing regimen under drug interaction scenarios (i.e., CYP3A inhibitors and CYP2B6 substrate)
4. Management of potential residual effects of lemborexant (e.g., somnolence) post-dose.

Recommendations
The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in NDA 212028 to support an approval of lemborexant. The acceptability of specific drug information is provided below.

Table 23: Acceptability of Specific Drug Information to Support Approval of Lemborexant

Decision	Acceptable to OCP?	Comments
Overall	☑ Yes ☐ No ☐ NA	Pending labeling agreement
General dosing instructions	☑ Yes ☐ No ☐ NA	The recommended dose of lemborexant is 5 mg, taken no more than once daily and immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. If the 5 mg dose is well-tolerated but greater effect is needed, the dose can be increased to 10 mg once per night. The maximum recommended dose is 10 mg once daily.
Dosing in patient subgroups (intrinsic and extrinsic factors)	☑ Yes ☐ No ☐ NA	Findings: Intrinsic factors: In general, no dose adjustment is necessary in patients based on age, gender, race and renal impairment. Hepatic impairment: Use of lemborexant is not recommended for use in subjects with severe hepatic impairment (Child-Pugh class C). Recommend capping the dose of lemborexant at 5 mg for subjects with moderate hepatic impairment. Subjects with mild hepatic impairment should be cautious about higher risk of somnolence. Renal impairment: Subjects with severe renal impairment should be cautious about higher risk of somnolence. Extrinsic factors: CYP3A inhibitors: Recommend avoiding concomitant use of strong or moderate CYP3A inhibitors with lemborexant. Recommend capping the dose at 5 mg when concomitant use with weak CYP3A inhibitors. CYP3A inducers: Recommend avoiding concomitant use of strong or moderate CYP3A inducers. CYP2B6 substrates: Co-administration of CYP2B6 substrates with lemborexant could result in decrease (up to 2-fold) in the AUC of CYP2B6 substrates, possibly requiring a proportional dosage increase or monitoring for clinical response. Alcohol: Recommend avoiding alcohol consumption with lemborexant. Food effect: Time to sleep onset may be delayed if taken with or soon after a meal.
Labeling	☑ Yes ☐ No ☐ NA	Pending satisfactory agreement with the Applicant.

Abbreviations: AUC, area under the curve; CYP, cytochrome p450

Post-Marketing Requirements and Commitments

1. Conduct an in vitro DDI study to assess the potential of lemborexant as an inducer for CYP2C8, CYP2C9 and CYP2C19.
2. Conduct an in vitro DDI study to assess the potential of lemborexant as an P-gp substrate at clinically relevant concentrations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

In the current submission, the Applicant has submitted 20 clinical studies of which 16 are phase 1 clinical pharmacology studies. These studies investigated the PK of lemborexant, the elimination pathways, the effects of intrinsic and extrinsic factors on lemborexant PK, the abuse liability and assessed the relationship between lemborexant PK and PD related to clinical efficacy and safety. The potential for lemborexant to prolong the QT interval was assessed based on data from two phase 1 PK studies. In addition, the submission contains 17 *in vitro* studies evaluating metabolism, protein binding and metabolic based drug-drug interactions (DDI). Population pharmacokinetic analysis and physiologically based pharmacokinetic analysis are also included in the submission. The Applicant reported that efficacy/safety for lemborexant was demonstrated by 2 adequate and well-controlled phase 3 studies (303 and 304) and supported by a phase 2 dose ranging study (201). Summarized below are the key clinical pharmacology findings from the submitted studies.

Absorption

The time to peak concentration (t_{max}) of lemborexant is approximately 1 to 3 hours.

Effect of Food

Lemborexant C_{max} decreased by 23%, $AUC_{0\text{-}inf}$ increased by 18%, and t_{max} was delayed by 2 hours following administration of a high-fat and high-calorie meal (containing approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively).

Distribution

The apparent volume of distribution (V/F) of lemborexant is approximately 1970 L. Protein binding of lemborexant is approximately 93.2% to 94.0% between 29 ng/mL and 71 ng/mL. Blood to plasma concentration ratio of lemborexant is 0.65.

Elimination

Metabolism

Lemborexant is primarily metabolized by CYP3A4, and to a less extent by CYP3A5. The major circulating metabolite is M10.

Excretion
Following administration of an oral dose, 57.4% of the dose was recovered in the feces and 29.1% in the urine (<1% as unchanged). The effective half-live for lemborexant (5 mg and 10 mg) is approximately 18 hours.

Intrinsic Factors
No clinically significant difference in the pharmacokinetics of lemborexant was observed based on age, sex, race/ethnicity, and body mass index (BMI). No study has been conducted to investigate the pharmacokinetics of lemborexant in pediatric patients.

Hepatic Impairment:
The effect of severe hepatic impairment (Child-Pugh class C) on lemborexant pharmacokinetics has not been studied.

- Lemborexant C_{max} and $AUC_{0\text{-}inf}$ were 22% and 54% higher in subjects with moderate hepatic impairment (Child-Pugh class B) as compared to healthy subjects. The terminal $t_{1/2}$ was prolonged from 67 hours in healthy subjects to 105 hours in subjects with moderate hepatic impairment.
- Lemborexant C_{max} and $AUC_{0\text{-}inf}$ were 58% and 25% higher in subjects with mild hepatic impairment (Child-Pugh class A) as compared to healthy subjects. The terminal $t_{1/2}$ was similar between subjects with mild hepatic impairment and healthy subjects.

Renal Impairment:

- Lemborexant exposure in subjects with severe renal impairment was 51% higher for $AUC_{0\text{-}inf}$, but did not affect C_{max} compared to subjects with normal renal function. The terminal $t_{1/2}$ was similar between subjects with mild hepatic impairment and healthy subjects.

Drug Interactions:
Clinical Studies and Model-Informed Approaches
CYP Enzyme Inhibitors:

- Concomitant use of itraconazole (a strong CYP3A inhibitor) increased lemborexant C_{max} by 1.4-fold and $AUC_{0\text{-}inf}$ by 3.7-fold.
- Concomitant use of fluconazole (a moderate CYP3A inhibitor) increased lemborexant C_{max} by 1.6-fold and $AUC_{0\text{-}inf}$ by 4.2-fold.
- PBPK model predicted that concomitant use of ranitidine (a weak CYP3A inhibitor) increased lemborexant C_{max} by 1.13-fold and AUC by 1.58-fold.

CYP Enzyme Inducers:

- Concomitant use of rifampin (a strong CYP3A inducer) decreased lemborexant C_{max} and $AUC_{0\text{-}inf}$ by 91% and 97%, respectively.

CYP Enzyme Substrates:

- A single-dose of midazolam (a CYP3A substrate) exposure was not affected by coadministration with lemborexant dosed under steady-state conditions.
- Coadministration of a single-dose of bupropion (a CYP2B6 substrate) with steady-state lemborexant decreased the C_{max} and $AUC_{0\text{-}inf}$ of S-bupropion by 49.9% and 45.5%, and decreased the C_{max} and $AUC_{0\text{-}inf}$ of [S, S]-hydroxylated bupropion by 17% and 24.5%, respectively.

Alcohol:

- Concomitant use of alcohol increased lemborexant C_{max} and $AUC_{0\text{-}72h}$ by 35% and 70%, respectively. Concomitant use of lemborexant did not affect alcohol concentrations.
- Lemborexant coadministered with alcohol produced a statistically significantly greater negative effect on postural stability as compared with alcohol alone at approximately t_{max} of lemborexant (2 hours) post-dose.
- Lemborexant co-administered with alcohol is associated with numerically greater negative impact on cognitive performance as compared with alcohol alone at approximately t_{max} of lemborexant (2 hours). Values for cognitive performance returned to baseline by 9 hours post-dose.

Anti-Acid Drugs:

- No clinically significant difference in lemborexant pharmacokinetics was observed when used concomitantly with famotidine (H_2 blocker).

Oral Contraceptives:

- No clinically significant pharmacokinetic difference was observed for either lemborexant or oral contraceptives containing norethindrone (NE) and ethinyl estradiol (EE) when used concomitantly.

General Dosing

The recommended dose of lemborexant is 5 mg, taken no more than once daily and immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. If the 5 mg dose is well-tolerated but greater effect is needed, the dose can be increased to the maximum recommended dose of 10 mg once per night.

Therapeutic Individualization

- *Hepatic Impairment:*

  Use of lemborexant is not recommended for use in subjects with severe hepatic impairment (Child-Pugh class C).

  The recommended dose for subjects with moderate hepatic impairment (Child-Pugh class B) is 5 mg.

Subjects with mild hepatic impairment (Child-Pugh class A) should be cautious about higher risk of somnolence.

- *Renal Impairment:*

  Subjects with severe renal impairment should be cautious about higher risk of somnolence.

- *Coadministration with Strong, Moderate or Weak CYP3A Inhibitors*

  Avoid concomitant use of lemborexant with strong or moderate CYP3A inhibitors.

  The recommended dose of lemborexant is 5 mg when concomitant use with weak CYP3A inhibitors.

- *Coadministration with CYP3A Inducers*

  Avoid concomitant use of lemborexant with strong or moderate CYP3A inducers.

- *CYP2B6 Substrates*

  Coadministration of substrates of CYP2B6 with lemborexant could result in decrease (up to 2-fold) in the AUC of CYP2B6 substrates, possibly requiring a proportional dosage increase or clinical monitoring.

- *Alcohol*

  Recommend avoiding alcohol consumption with lemborexant.

- *Food Effect*

  Time to sleep onset may be delayed if taken with or soon after a meal.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 24: General Pharmacology and Pharmacokinetic Characteristics

Pharmacology		
Mechanism of Action	The mechanism of action of lemborexant to treat insomnia, characterized by difficulties with sleep onset and/or sleep maintenance is unclear. However, lemborexant is an orexin receptor antagonist. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.	
Pharmacodynamics	Lemborexant is a competitive antagonist for OX1R and OX2R, with a higher affinity for OX2R. A major metabolite of lemborexant, M10, binds with comparable affinity to OX1R and OX2R as the parent drug. However, considering that the unbound systemic exposure of M10 is significantly lower as compared to parent drug and M10 is a P-gp substrate with less brain penetration as compare to parent drug, lemborexant is believed to be the main contributor to the pharmacologic activities in humans and the contributions of its metabolites are predicted to be low.	
QT Prolongation	In a concentration-QT analysis using the data from two randomized, double-blind, placebo-controlled, multiple ascending dose studies in healthy subjects, treatment of lemborexant did not prolong the QT interval at doses of up to 7.5 times the maximum recommended dose of 10 mg (C_{max} approximately 400 ng/mL).	
General Information		
Bioanalysis	LC-MS/MS method was used for the quantitation of lemborexant and its three metabolites M4, M9 and M10 in human plasma after lemborexant administration. This bioanalytical method is validated and considered acceptable.	
Healthy Volunteers vs. Patients	PK is similar between patients and healthy subjects.	
Drug exposure at steady-state following the therapeutic dosing regimen	The mean steady-state $AUC_{0-\tau}$ and C_{max} of lemborexant following 10 mg QD dosing are 357 to 446 ng·h/ mL and 47 to 65 ng/mL, respectively.	
Maximum tolerated dose or exposure	Single Dose	200 mg was the highest dose tested; and MTD was not achieved.
	Multiple Dose	75 mg QD dosing of lemborexant for 14 days was the highest dose tested; and MTD was not achieved.

Pharmacology	
Dose Proportionality	The exposure of lemborexant increases slightly less than dose-proportionally from 2.5 to 75 mg.
Variability	The inter-subject variability for apparent clearance is 48%.
Accumulation	Following multiple dosing, the extent of accumulation of lemborexant at steady-state was 1.5- to 2-fold
Absorption	
T_{max}	Approximately 1 to 1.5 hours post-dose for the 5 and 10 mg doses.
Absolute bioavailability	The absolute bioavailability of lemborexant in humans has not been not determined.
Distribution	
V/F	1970 L
Protein Binding	93.2% to 94.0%
Substrate of transporter systems	Lemborexant is a potential poor substrate for P-gp and is not a substrate for BCRP Lemborexant is not a substrate for OATP1B1 and OATP1B3.
Elimination	
$T_{1/2}$	The effective half-life based on accumulation was approximately 17 and 19 hours for the 5 and 10 mg doses.
Metabolism	
Primary Metabolizing enzymes	Lemborexant is mainly metabolized by CYP3A4, followed to a less extent by CYP3A5.
Inhibitor/Inducer	Lemborexant and M10 have a potential to induce CYP3A and CYP2B6, and a weak potential to inhibit CYP3A. Lemborexant and M10 do not inhibit other CYP isoforms or transporters (P-gp, BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K).
Excretion	
Primary excretion pathways	Metabolism by CYP3A

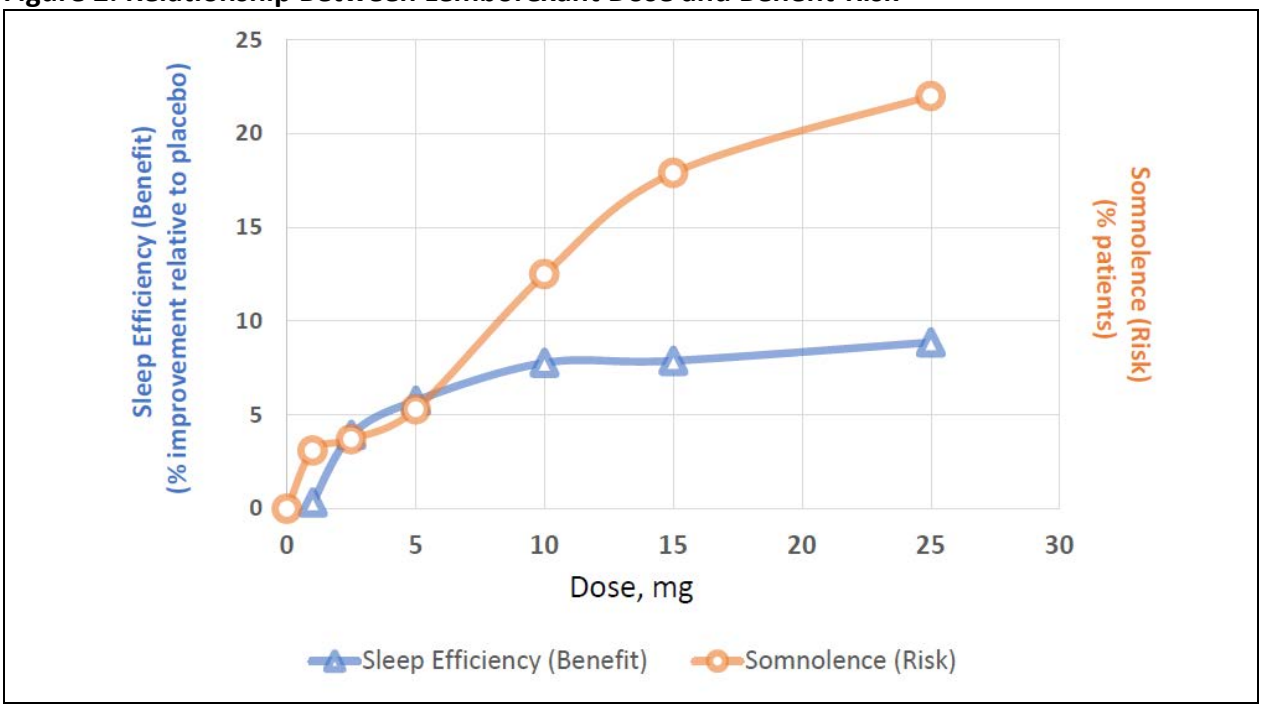
Abbreviations: AUC_{0-T}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CYP, cytochrome P450; BCRP, breast cancer resistance protein; BSEP, Bile Salt Export Pump; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MATE, multi-antimicrobial extrusion protein; MTD, maximum tolerated dose; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PK, pharmacokinetics; P-gp, P-glycoprotein; QD, once daily; $T_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; V/F, apparent volume of distr bution

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Yes. The proposed dosing regimen is appropriate for the general population and doses higher than 10 mg are unlikely to offer adequate balance of benefit and risk. Figure 2 shows the relationship between benefit (average improvement in sleep efficiency relative to placebo) and risk (percentage of patients with somnolence). The incidence of somnolence is 5.3% at 5 mg and 12.5% at 10 mg when compared to 17.9% and 22% at 15 and 25 mg. The data suggests that while greater improvements in sleep efficiency are not observed at doses greater than 10 mg, the risk for somnolence continue to increase with doses greater than 10 mg.

Figure 2: Relationship Between Lemborexant Dose and Benefit-Risk



Note: Benefit is defined as "average improvement in sleep efficiency relative to placebo." Risk is defined as proportion of patients with "somnolence" benefit.
Source: Reviewer's analysis based on findings reported by the Applicant in e2006-g000-201-study-report-body.pdf

6.3.2.2. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (i.e., Age, Weight, Organ Impairments etc.)?

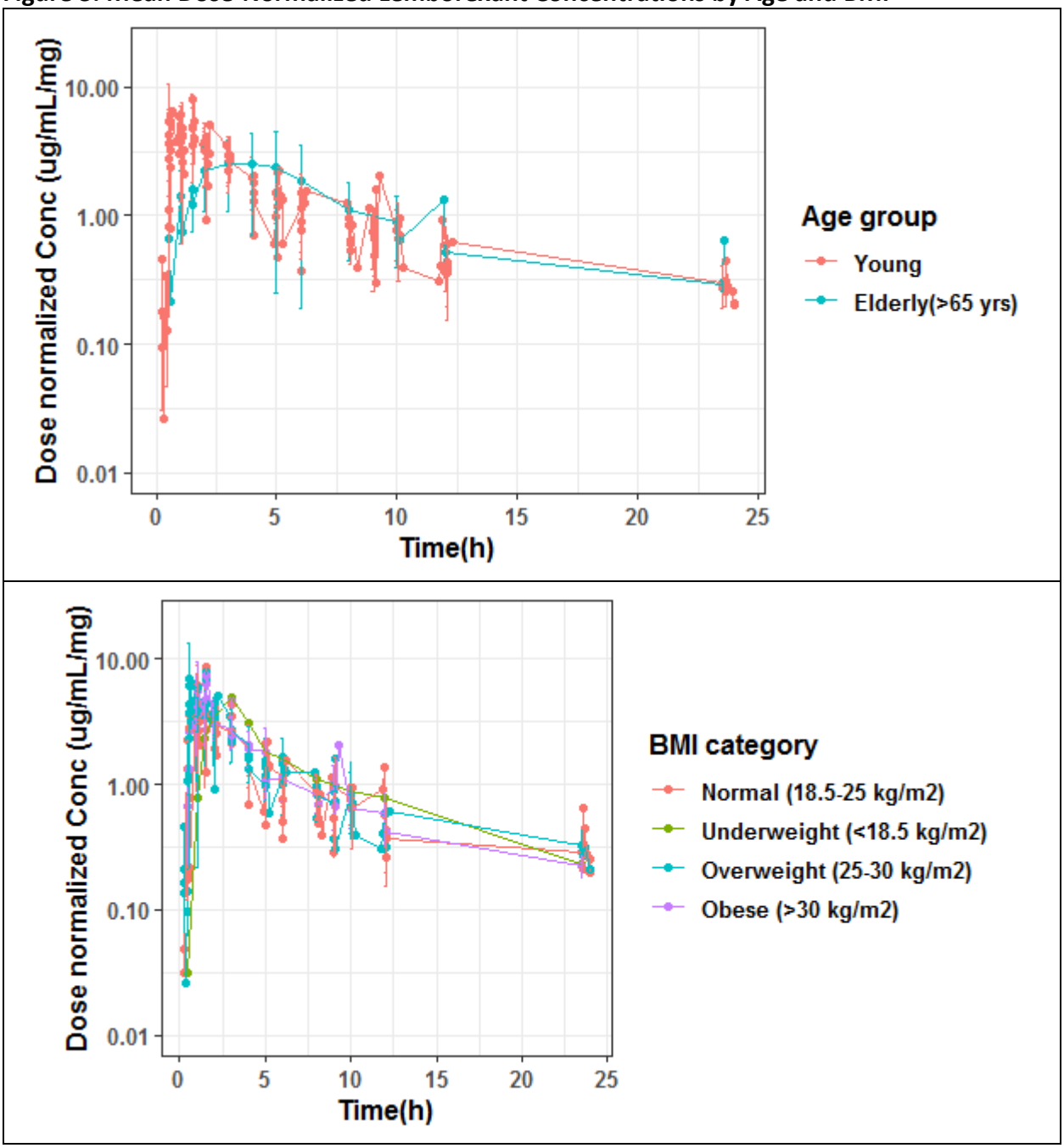
No

Effect of Age, BMI, Race and Sex

Dose adjustments are not required for subpopulations based on intrinsic patient factors of age, BMI, race and sex.

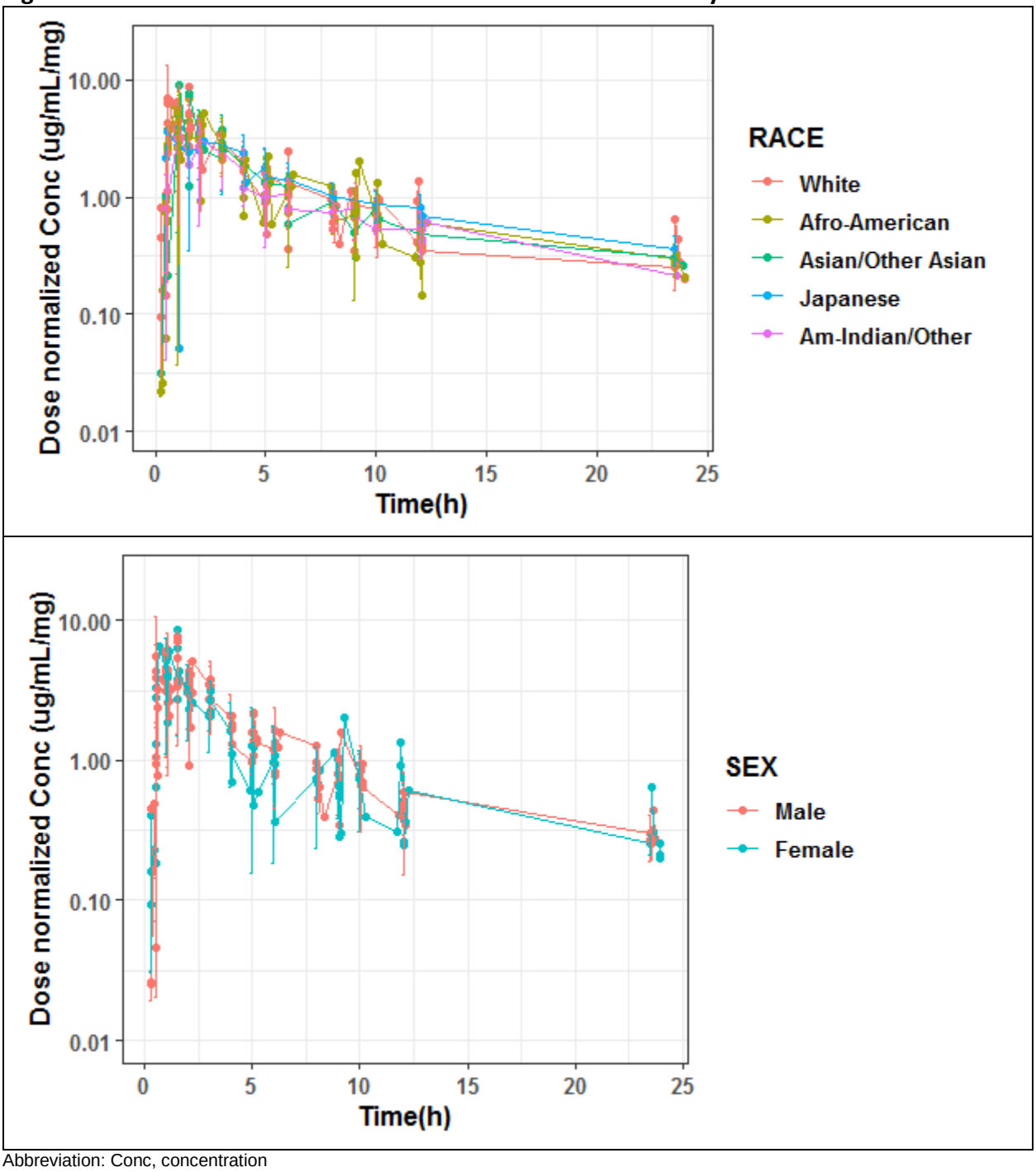
Figure 3 and Figure 4 below show the concentration-time profiles of lemborexant for various intrinsic patient factors.

Figure 3: Mean Dose-Normalized Lemborexant Concentrations by Age and BMI



Abbreviations: BMI, body mass index; Conc, concentration
Source: Reviewer's analysis

Figure 4: Mean Dose-Normalized Lemborexant Concentrations by Race and Sex



Abbreviation: Conc, concentration
Source: Reviewer's analysis

Applicant's population pharmacokinetic analyses showed that:

- Lower lemborexant clearance was observed in elderly subjects (age ≥ 65 years) compared to adults
- Higher BMI was associated with lower lemborexant clearance
- Neither race nor sex had an effect on lemborexant clearance

Refer to Section 14.4.1, Population Pharmacokinetics Analysis for more details.

No dose adjustments are proposed based on age, BMI, race and sex.

Effect of Hepatic Impairment

The effect of hepatic impairment on the PK of lemborexant was evaluated in Study 104 in subjects with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B).

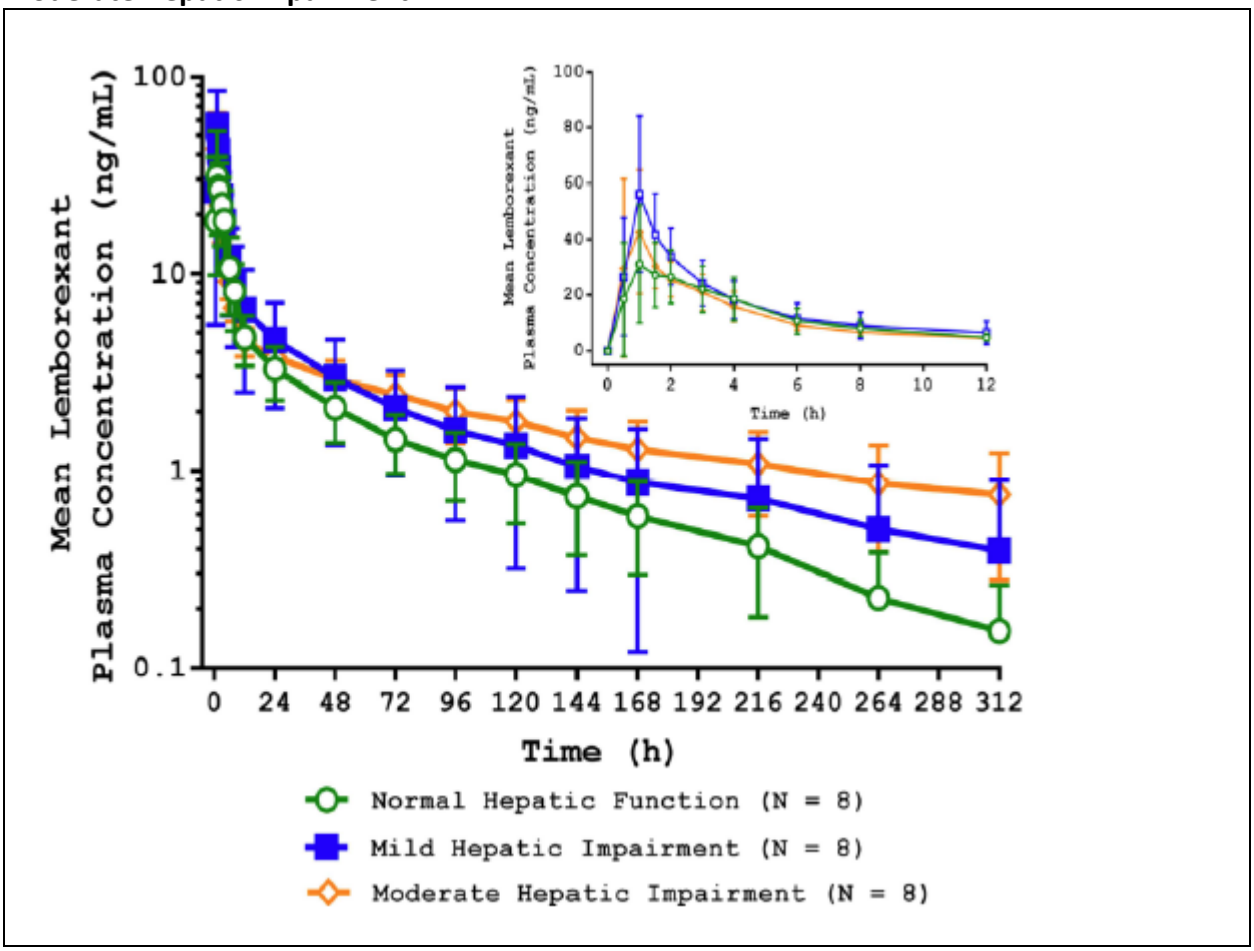
The unbound fraction of lemborexant in plasma was similar in subjects with mild or moderate hepatic impairment and healthy subjects (f_u=0.060 to 0.065), indicating that hepatic impairment does not affect protein binding of lemborexant.

Lemborexant C_{max} and $AUC_{0\text{-}inf}$ were 58% and 25% higher in subjects with mild hepatic impairment (Child-Pugh Class A), and 22% and 54% higher in subjects with moderate hepatic impairment (Child-Pugh Class B), compared to healthy subjects following a single dose of 10 mg lemborexant. The terminal half-lives were 1.1- and 1.6-fold longer in subjects with mild (73.7 hours) and moderate hepatic impairment (105 hours), as compared to healthy subjects (67.0 hours). As a result, subjects with mild (2.7-fold accumulation) and moderate (3.9-fold accumulation) hepatic impairment are expected to have higher accumulation ratios as compared to healthy subjects (2.25-fold accumulation). According to dose-benefit/risk relationship for lemborexant, a 50% and 100% increase of maximum dose is expected to result in 5.4% and 9.5% increase in the percentage of patients with somnolence. The mean plasma concentrations of lemborexant 8 hours post-dose were similar for subjects with moderate hepatic impairment (6.71 ng/mL) and normal hepatic function (8.14 ng/mL), indicating a weak potential for residual effect of somnolence.

Therefore, the lemborexant dose is recommended to be capped at 5 mg in subjects with moderate hepatic impairment. Dose adjustment is not warranted for subjects with mild hepatic impairment; however, these subjects should be aware of the potential increased risk of somnolence due to increased lemborexant exposure.

The influence of hepatic impairment on the PK of lemborexant has not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C), and thus dosing in the severe category is not recommended.

Figure 5: Pharmacokinetic Profiles of Lemborexant in Subjects With Normal, Mild and Moderate Hepatic Impairment



Source: Reviewer's analysis

Effect of Renal Impairment

The effect of renal impairment on the PK of lemborexant was evaluated in Study 105 in subjects with severe renal impairment (eGFR between 15 to 29 mL/min/1.73 m^2 and not on dialysis) following a single dose of 10 mg lemborexant.

Mean lemborexant C_{max} was similar between subjects with severe renal impairment and subjects with normal renal function following a single-dose of lemborexant. The mean lemborexant AUC_{0-t} and AUC_{0-inf} were 1.5-fold higher for subjects with severe renal impairment compared to subjects with normal renal function. The terminal half-life for lemborexant was similar between subjects with severe renal impairment (72.9 hours) and subjects with normal renal function (67.8 hours). The mean f_u was approximately 7% for both groups.

According to dose-benefit/risk relationship for lemborexant, a 50% dose increase is expected to result in 5.4% increase in the percentage of patients with somnolence. Although dose

adjustment may not be warranted, patients with severe renal impairment should be cautious about higher risk for somnolence.

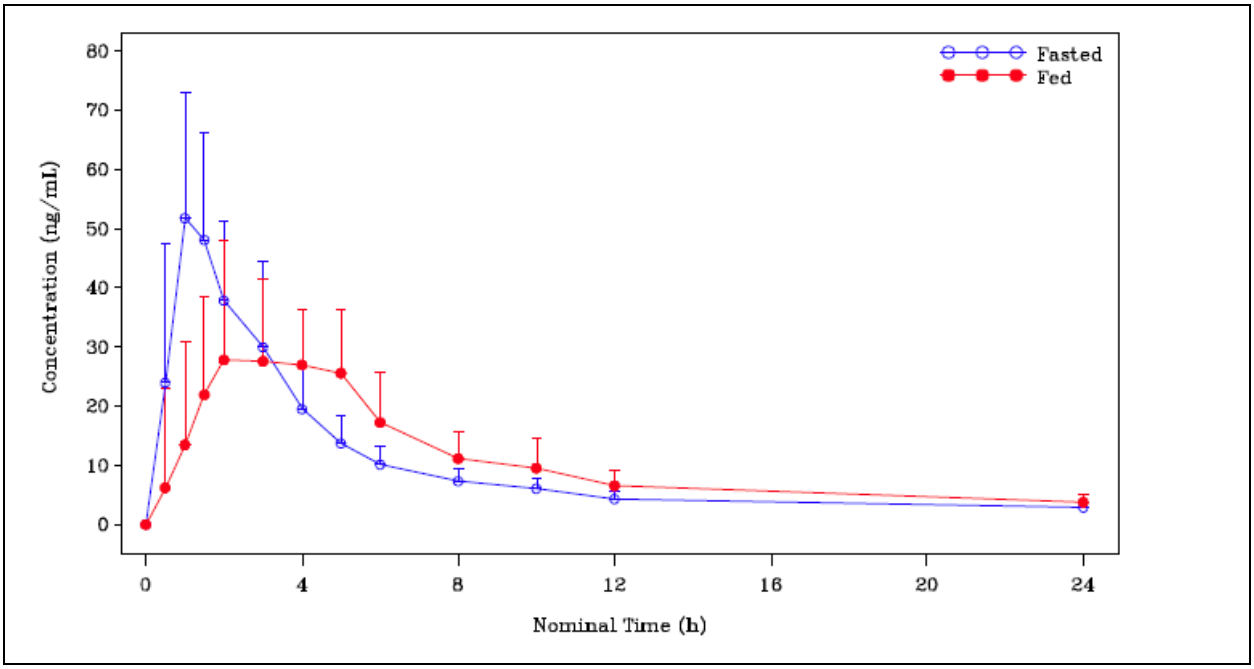
6.3.2.3. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food

The effect of a high-fat and high-calories meal on the rate and extent of lemborexant absorption following a single oral dose of 10 mg lemborexant in healthy subjects was evaluated in Study 008. Ingestion of lemborexant with a high-fat and high-calorie meal (approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat) resulted in 23% decrease in C_{max}, and 18% increase in AUC_{0-t} and AUC_{0-inf}. T_{max} was delayed by 1.75 hours from fasting to fed conditions (Figure 6). The terminal $t_{1/2}$ was similar with (53.8 hours) and without (50.8 hours) food consumption with lemborexant. The mean plasma concentrations of lemborexant 8 hours post-dose were similar for fed (10.3 ng/mL) and fasting groups (7.02 ng/mL), indicating a weak potential for residual effect of somnolence.

However, due to delay of T_{max} following food intake, time to sleep onset may be delayed if taken with or soon after a meal. Also in the phase 3 studies (303 and 304), subjects were not allowed to eat a meal within 3 hours before taking lemborexant.

Figure 6: Mean Plasma Concentration-Time Curve of Lemborexant Over 0 to 24 Hours by Treatment



Source: Applicant's Study Report 008. Figure 4. Page 60

DDI Liability From In Vitro Studies

Lemborexant as a substrate for CYPs:

- *In vitro* metabolism studies indicated that lemborexant is eliminated by metabolism primarily via CYP3A, so there is a potential for drug interaction between lemborexant and inhibitors and/or inducers of CYP3A.

Lemborexant and/or its metabolites as a CYP inducer or inhibitor:

- Lemborexant and its metabolites (M4, M9 and M10) have modest induction effects on CYP3A4 and CYP2B6 *in vitro* in human hepatocytes, so there is a potential for drug interaction between lemborexant and substrates of CYP3A and CYP2B6. In addition, since both CYP3A4/5 and CYP2C enzymes are induced via activation of the pregnant X receptor (PXR), we recommend further evaluating the potential of lemborexant to induce CYP2C8, CYP2C9 and CYP2C19.
- Lemborexant and its metabolites (M4, M9 and M10) showed minimal or no induction effect on CYP1A2, which is unlikely translated into any clinically relevant DDIs.
- Lemborexant demonstrated reversible inhibition of CYP2A6 (IC_{50}: 7.8 μM) and CYP2C19 (IC_{50}: 24.6 μM), and time-dependent inhibition of CYP3A (K_i: 25.2 μM). Lemborexant and its major metabolites did not inhibit other CYP enzymes. The inhibition effects of lemborexant on CYP2A6, CYP2C19 and CYP3A are unlikely translated into any clinically relevant DDIs.
- Lemborexant and its metabolites M4, M9, and M10 also showed a mild activating effect (≤ 2.1-fold) on CYP2E1 and time-dependent inhibition potency on CYP3A at 3 μmol/L or higher. This activating effect on CYP2E1 is unlikely translated into any clinically relevant DDIs.

Lemborexant as a transporter substrate:

- Lemborexant was determined to be a poor substrate of P-gp at higher than clinically relevant concentration (3 μM). The in vitro testing concentration of 3 μM for lemborexant is 300-fold higher than clinically relevant concentration (unbound C_{max}: 10 nM). At high concentration, there is a potential for P-gp been saturated and the reported efflux ratio may have been underestimated. Thus, we recommend re-conducting an *in vitro* DDI study to assess the potential of lemborexant as a substrate for P-gp substrate at clinically relevant concentrations.
- Lemborexant is not a substrate of breast cancer resistance protein (BCRP), OATP1B1 or OATP1B3.
- M10 is a substrate of P-gp but not BCRP.

Lemborexant and its metabolites as transporter inhibitors:

- Lemborexant and some of its metabolites (i.e., M4, M9 and M10) showed inhibition on BSEP, MATE1, MATE2-K, OATP1B1, OATP1B3, OAT3, OCT1, and OCT2 with IC_{50} values ranging from 7.4 to 32.2 μM. These IC_{50} values are much higher than clinically relevant concentrations, thus it is unlikely translated into any clinically relevant DDIs. Lemborexant did not inhibit OAT1.

DDI Liability From Clinical Studies

Effect of Other Drugs on the PK of Lemborexant

- Inhibitors of CYP3A Enzyme Activity

Strong CYP3A Inhibitors:

The effect of itraconazole (strong CYP3A inhibitor) on the PK of lemborexant was evaluated in Study 1004. Healthy subjects were administered a single oral dose of 10 mg lemborexant. After washout, itraconazole (200 mg, capsule formulation) was administered QD consecutively for 20 days under fasting conditions and a single dose of 10 mg lemborexant was administered on Day 8 after starting itraconazole dosing.

The lemborexant C_{max}, AUC_{0-t} and AUC_{0-inf} values increased by approximately 1.4-, 3.6- and 3.7-fold, respectively as compared with the administration of 10 mg lemborexant alone (Figure 7). According to the dose-benefit/risk relationship (Figure 2), the significant increase in lemborexant exposure when coadministered with a strong CYP3A inhibitor is expected to increase risk of somnolence. Thus, we recommend avoiding concomitant use of lemborexant with strong CYP3A inhibitors.

It is noticed that the extent of increase in lemborexant exposure (< 5-fold) when coadministered with itraconazole is less than those reported for probe CYP3A substrates (e.g., midazolam). When coadministered with ketoconazole, midazolam exposure increased 5- to 19-fold. The extent of increase for lemborexant when coadministered with itraconazole is also less than that when coadministered with fluconazole (a moderate CYP3A inhibitor). One of the potential reasons is that the Applicant did not conduct the DDI study using the optimized formulation (capsule *vs* solution) and food conditions (fasting *vs* fed) for itraconazole to achieve maximum inhibition for CYP3A. Capsule itraconazole administered under fasting conditions was reported to have a relatively lower exposure as compared to that under fed conditions at the same dose level, and it was also lower than that observed for solution under both fasting and fed conditions (Table 25) [15]. As in our DDI study, capsule itraconazole was used under fasting conditions, thus it is possible that the DDI study between lemborexant and itraconazole may not represent the worst-case scenario of CYP3A inhibition effect from itraconazole.

Table 25: Itraconazole (ITZ) and Hydroxy-Itraconazole (OH-ITZ) PK Parameters Following a Single Oral Dose of Itraconazole Capsules or Solution Administered Under Fasting or Fed Conditions

	ITZ capsule (200 mg)		ITZ solution (200 mg)	
PK Parameters	**Fasting**	**Fed**	**Fasting**	**Fed**
C_{max} (ng/mL)	140 (65)	239 (85)	546 (22)	307 (22)
AUC_{inf} (ng*h/mL)	2094 (905)	3415 (1153)	4520 (160)	3162 (160)

Abbreviations: C_{max}, maximum plasma concentration; ITZ, itraconazole; OH-ITZ, hydroxy-itraconazole; PK, pharmacokinetics; AUCinf, AUCinf is a theoretical measure of the total exposure of drug to the body from administration till all the drug is eliminated.
Source: Liu, L; et al. 2016. J Clin Pharmacol

Moderate CYP3A Inhibitors:
The effect of fluconazole (a moderate CYP3A inhibitor) on the PK of lemborexant was evaluated in Study 012. Healthy subjects were administered a single oral dose of 10 mg lemborexant under fasting conditions. After 10-days washout, on Day 11, subjects were administered fluconazole 400 mg followed by fluconazole 200 mg QD from Days 12 to 26. A single dose of lemborexant 10 mg was administered following an overnight fasting along with fluconazole on Day 15. The lemborexant C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values increased by approximately 1.6-, 3.8- and 4.2-fold, respectively, as compared with lemborexant alone (Figure 7). According to the dose-benefit/risk relationship (Figure 2), the significant increase in lemborexant exposure when coadministered with a moderate CYP3A inhibitor is expected to increase risk of somnolence. Thus, we recommend avoiding concomitant use of lemborexant with moderate CYP3A inhibitors.

Weak CYP3A Inhibitors:
The effect of weak CYP3A inhibitors on the PK of lemborexant was evaluated by the PBPK modeling and simulation. The simulation results predicted that fluoxetine (40 mg QD) increased the C_{max} and $AUC_{0\text{-}t}$ values of lemborexant by 1.2- and 1.8-fold, respectively.

After reviewing the Applicant's submission and relevant literatures, the review team determined that fluoxetine is not a CYP3A inhibitor or a very weak inhibitor (increases CYP3A substrates exposure by up to 25%) for the following reasons:

- Although *in vitro* studies suggested that the enantiomers of fluoxetine and norfluoxetine are weak CYP3A inhibitors, clinical DDI studies suggested that multiple doses of fluoxetine had no effect on midazolam, triazolam, lovastatin and quetiapine (prob CYP3A substrates) exposures (University of Washington DDI database). The *in vitro* data over-predicted the DDI liabilities with CYP3A substrate by fluoxetine.
- Fluoxetine was reported to decrease alprazolam (a moderately sensitive CYP3A substrate) clearance by 21% and increase AUC by 26.6%, which was marginally above the threshold of 25% that is consider a positive DDI study. Even considering this as a positive DDI study, the effect of fluoxetine on CYP3A substrate is expected to be weak.

- Sager's study [16] suggested that fluoxetine and norfluoxetine have very complicated inhibition-induction effects on multiple CYP enzymes, including inhibition of CYP2D6, CYP3A4 and CYP2C19 and induction for CYP3A. The mutual inhibitor-inhibitor interactions and CYP3A4 induction may explain the over-predicting results for CYP3A based on *in vitro* results.

Information request was sent to the Applicant (dated July 12, 2019) requesting clarification for using fluoxetine as a weak CYP3A inhibitor in the PBPK model. In the response letter (dated July 19, 2019), the Applicant stated that they are aware of fluoxetine been removed from the list of weak inhibitors in the FDA's 2017 DDI guidance (*https://www.fda.gov/media/108130/download*), due to recent reports of lacking clinical DDIs between fluoxetine and midazolam, triazolam or lovastatin. Thus, it is not appropriate to use fluoxetine to represent the weak CYP3A inhibitors in the DDI studies.

Subsequently, a new PBPK model simulating the DDI between lemborexant and ranitidine (as a weak CYP3 A inhibitor but not an acid-reducing agent) was submitted by the Applicant. The PBPK review team has reviewed the ranitidine model and confirmed that the model is adequate, and ranitidine can be used as a weak CYP3A inhibitor. The results show that the mean AUC and C_{max} of lemborexant are predicted to be increased by 1.6- and 1.1-fold, respectively, when coadministered with 150 mg twice daily ranitidine. Ranitidine is listed as a weak CYP3A inhibitor in the FDA's 2017 DDI guidance, and clinical studies reported that ranitidine increased the AUC and C_{max} of midazolam by 66% and 52%, respectively, and the AUC of triazolam by approximately 30% (University of Washington DDI database). The PBPK model of ranitidine can be used as one of the supporting evidences for dosing adjustment for lemborexant when coadministered with weak CYP3A inhibitors.

According to the FDA Guidance for Clinical Drug Interaction Studies (*https://www.fda.gov/media/82734/download*), a weak inhibitor is expected to increase the AUC of a sensitive index CYP substrate by ≥ 25% to < 100%, assuming the tested substrate is not more sensitive than known CYP3A substrates (e.g., midazolam and triazolam). In order to have a quantitative understanding of the sensitivity of lemborexant as a CYP3A substrate, lemborexant is compared to midazolam for the estimated hepatic extraction ratio (Eh).

The CL/F of lemborexant in adults is approximately 23 L/h based on the PopPK model. Assuming absolute bioavailability (Fa) of 1 (an overestimated value since ~13% of dose was recovered in feces as unchanged drug), the systemic plasma clearance of lemborexant is estimated to be 23 L/hr. Based on the reported blood to plasma ratio of 0.61, the blood clearance of lemborexant is 38 L/h (CL_{Blood} = CL_{Plamsa} / (B/P ratio) = 23/0.61). Given the reported human liver blood flow of 97 L/h, the Eh of lemborexant is estimated to be 0.39 (blood clearance/liver blood flow). Compared to the reported Eh value of midazolam of 0.46 [17], lemborexant has relatively smaller Eh and thus is unlikely to be more extensively metabolized than midazolam.

Therefore, lemborexant' s DDI liability as CYP3A substrate is unlikely to exceed that observed for midazolam. Lemborexant exposure is not expected to be increased more than 2-fold with any weak CYP3A inhibitors. According to the dose-benefit/risk relationship (Figure 2), the significant increase in lemborexant exposure is expected to be associated with increased risk of somnolence. We recommend capping the dose of lemborexant at 5 mg when concomitant use with weak CYP3A inhibitors.

- Inducers of CYP3A Enzyme Activity

Strong CYP3A Inducers:
The effect of rifampin (a strong CYP3A inducer) on the PK of lemborexant was evaluated in Study 1004. Healthy subjects were administered a single oral dose of 10 mg lemborexant. After washout, rifampin (600 mg) was administered QD consecutively for 20 days under fasting conditions and a single dose of 10 mg lemborexant was administered on Day 8 after starting rifampin dosing.

The lemborexant C_{max}, AUC_{0-t} and AUC_{0-inf} values decreased by approximately 92%, 97% and 97% as compared with the administration of 10 mg lemborexant alone (Figure 7). According to the dose-benefit/risk relationship (Figure 2), the significant decrease in lemborexant exposure when coadministered with a strong CYP3A inducer is expected to significantly affect lemborexant efficacy, and thus we recommend avoiding concomitant use of lemborexant with strong CYP3A inducers.

Moderate CYP3A Inducers:
There is no clinical study evaluating the effect of moderate CYP3A inducers on the PK of lemborexant. According to the FDA Guidance for Clinical Drug Interaction Studies (*https://www.fda.gov/media/82734/download*), a moderate inducer is expected to decrease the AUC of a sensitive index CYP substrate by ≥ 50% to < 80%. Thus, we recommend avoiding concomitant use of lemborexant with moderate CYP3A inducers.

Weak CYP3A Inducers:
There is no clinical study evaluating the effect of weak CYP3A inducers on the PK of lemborexant. According to the FDA Guidance for Clinical Drug Interaction Studies (*https://www.fda.gov/media/82734/download*), a weak inducer is expected to decrease the AUC of a sensitive index CYP substrate by ≥ 20% to < 50%, assuming the tested substrate is not more sensitive than known CYP3A substrates (e.g., midazolam and triazolam). As discussed in the weak CYP3A inhibitors section above, lemborexant is unlikely to be more extensively metabolized than midazolam. Moreover, lemborexant is allowed to be titrated from 5 mg to 10 mg based on efficacy response, a less than 50% decrease in lemborexant exposure when coadministered with weak CYP3A inducers is unlikely to result in significant loss of efficacy. Thus, dose adjustment is not warranted for lemborexant when concomitant use with weak CYP3A inducers.

- Gastric pH Modifier

The effect of famotidine (an H_2 blocker) on the PK of lemborexant was evaluated in Study 012. Healthy subjects were administered a single oral dose of 10 mg lemborexant under fasting conditions. After 15-days washout, subjects received a single dose of famotidine 40 mg followed by a single dose of lemborexant 10 mg at least 2 hours later under fasting conditions. The lemborexant C_{max} values decreased by approximately 27%, as compared with the administration of 10 mg lemborexant alone (Figure 7). AUC_{0-t}, AUC_{0-inf} and terminal $t_{1/2}$ values were similar with and without coadministration of famotidine.

A single-dose of famotidine is acceptable for DDI study, since famotidine is reported to have a quick gastric pH modification effect by increasing the gastric pH value above 4 at 2-hour post-dose [18]. In addition, lemborexant is reported to have a very high solubility at pH 1, and low but similar solubility between pH 3 and 6.8. Thus, although dedicated DDI study was not conducted, it is unlikely that proton pump inhibitors (PPIs) would have a different effect on the PK of lemborexant than H2 blockers. Thus, dose adjustment is not required when lemborexant is coadministered with gastric pH modifiers.

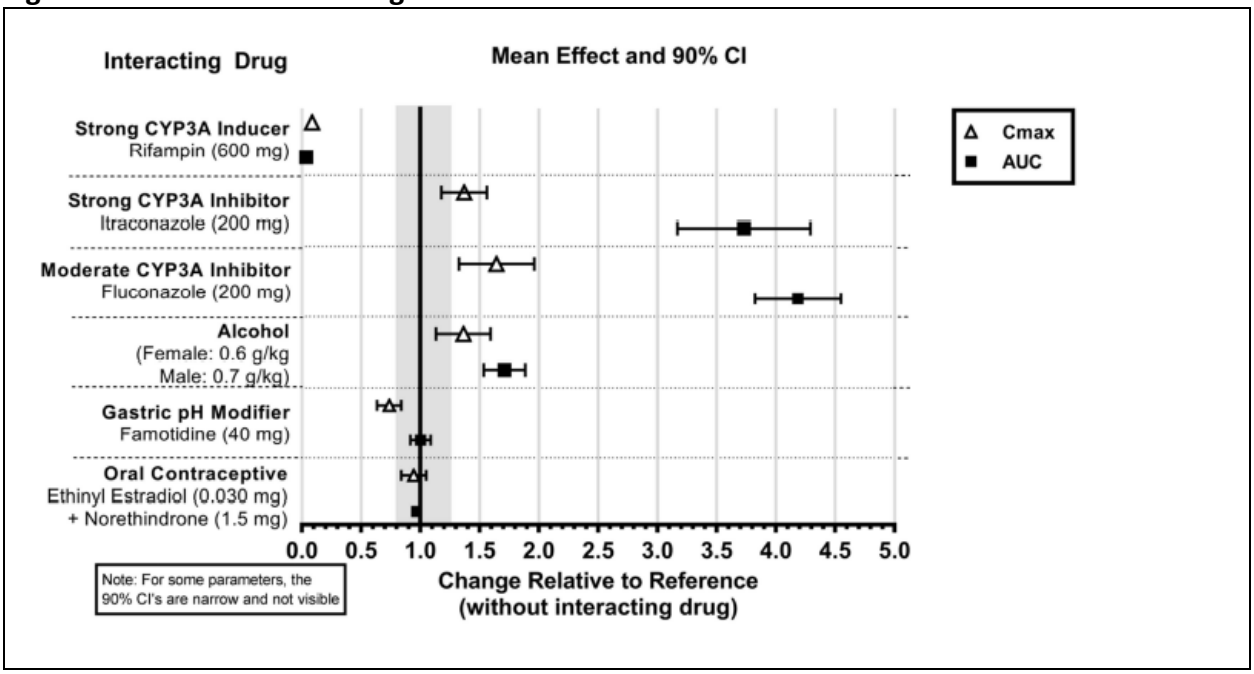
- Alcohol

The effects of alcohol on the PK, postural stability and cognitive performance of lemborexant oral tablet were evaluated in Study 009. Subjects were randomized to 1 of 4 treatment sequences and received a single dose of lemborexant 10 mg or placebo administered with or without alcohol (0.6 g/kg for females and 0.7 g/kg for males). PK of lemborexant was measured up to 72 hours post-dose. Postural stability was assessed using cognitive drug research posture assessment (body sway). Cognitive performance was assessed using computerized performance assessment battery, with four composite domain (power of attention, continuity of attention, quality of memory, and speed of memory retrieval) factor scores calculated. Blood alcohol assessments confirmed that subjects achieved blood alcohol levels that were higher than the 0.08% legal limit (i.e., 0.8 g/L) in the US when alcohol was administered alone or with lemborexant.

The results show that the coadministration of lemborexant with alcohol resulted in 35% and 70% increase in C_{max} and AUC_{0-72h} of lemborexant (Figure 7). The t_{max} and terminal $t_{1/2}$ were comparable for lemborexant when administered with or without alcohol.

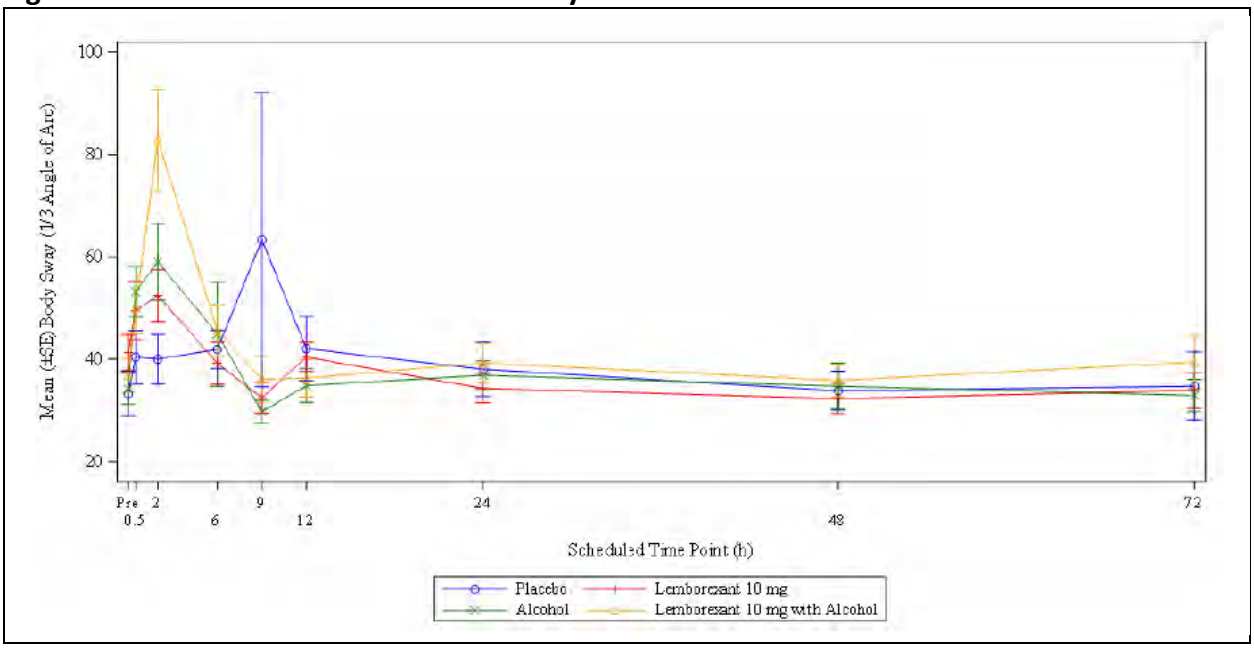
Both alcohol alone and lemborexant 10 mg produced significant decrease of postural stability at 2 hours (Figure 8). Lemborexant coadministered with alcohol produced a numerically greater negative impact on postural stability as compared with alcohol alone at approximately T_{max} of lemborexant (2 hours) post-dose.

Figure 7: Effects of Other Drugs on the Pharmacokinetics of Lemborexant



Abbreviations: AUC, area under the curve; CI, confidence interval, C_{max}, maximum plasma concentration
Source: Applicant's Summery of Clinical Pharmacology Studies, page 109, Figure 2.7.2.3.4-1

Figure 8: Measurement of Postural Stability Over Time



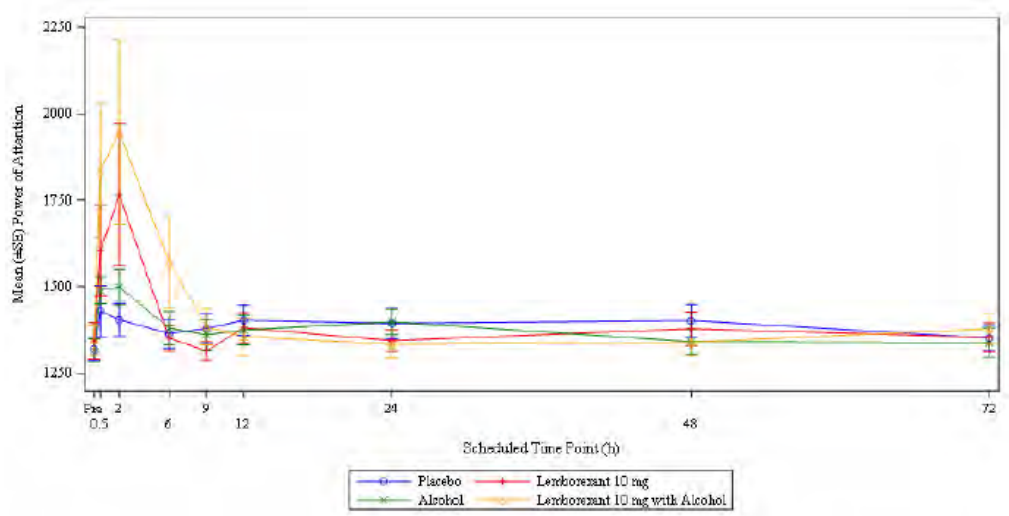
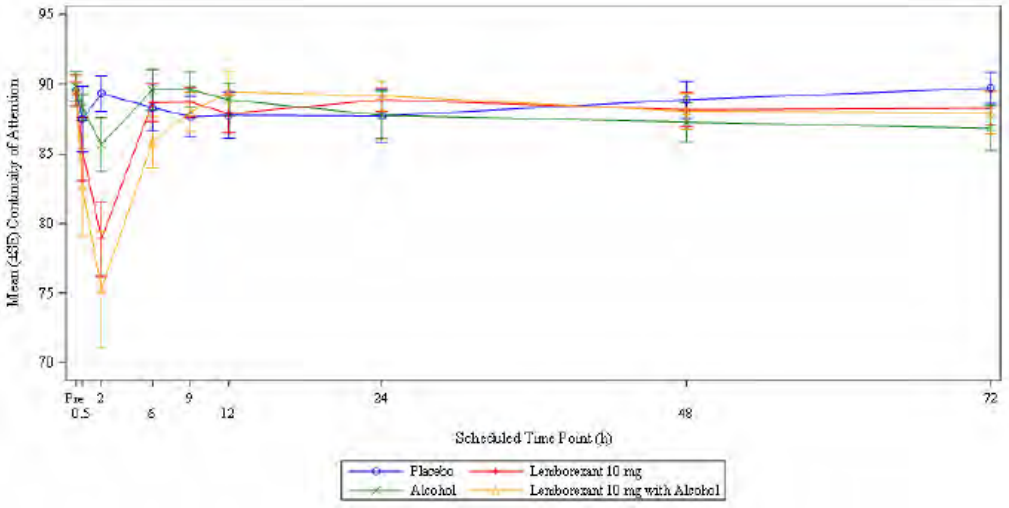
Abbreviation: sSE, subjective sleep efficiency
Source: Applicant's Clinical Study Report 009, page 83, Figure 7

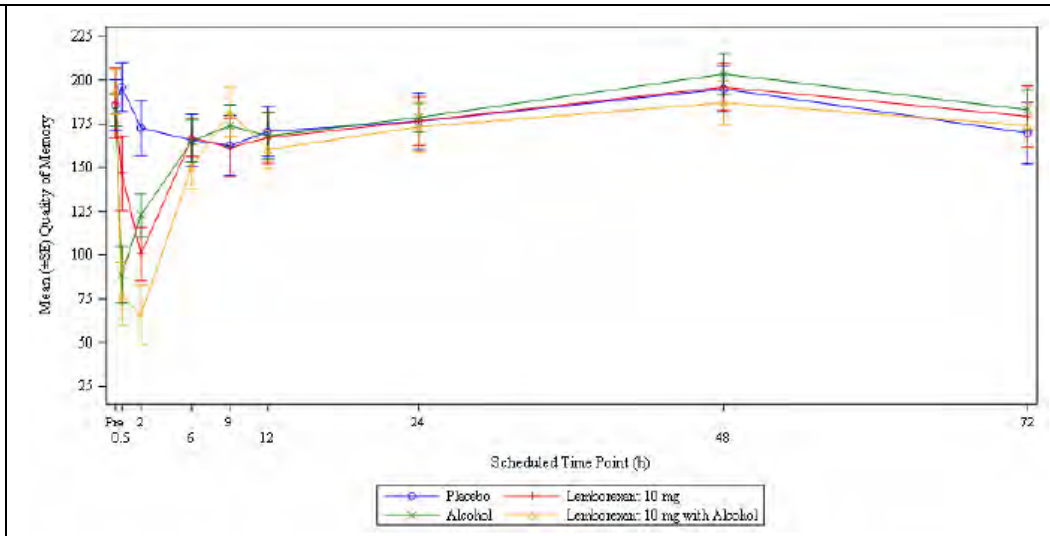
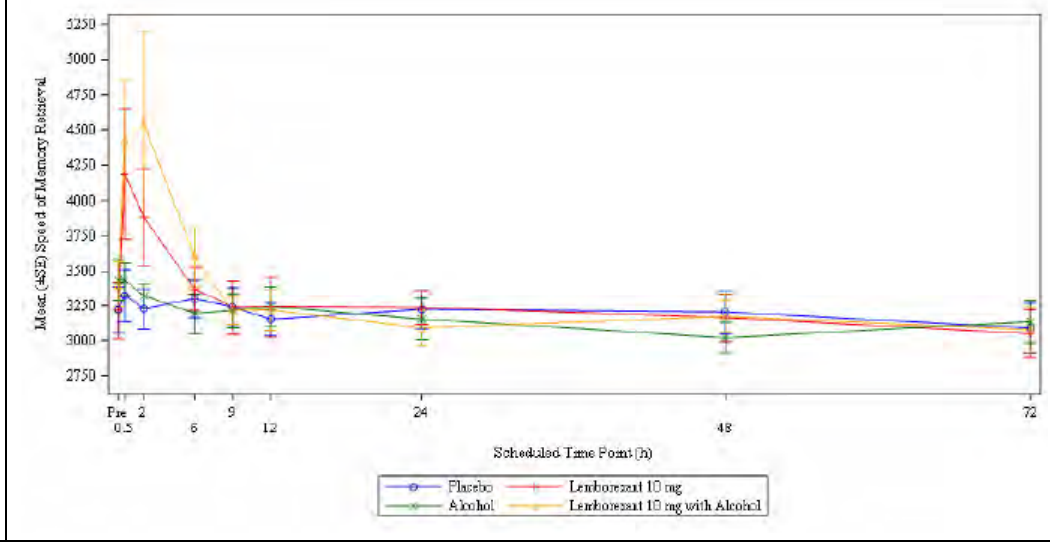
For cognitive performance assessment, lemborexant coadministered with alcohol was associated with numerically greater negative impact on cognitive performance (for all four

measures) compared to alcohol alone at approximately t_{max} of lemborexant (2 hours) (Figure 9). Values for cognitive performance returned to baseline by 9 hours post-dose.

Due to the risk of decreased cognitive performance when lemborexant coadministered with alcohol, we recommend avoiding alcohol consumption with lemborexant.

Figure 9: Measurement of Cognitive Performance by Treatments

Power of attention	
Continuity of attention	

Quality of memory	
Speed of memory	

Abbreviation: sSE, subjective sleep efficiency
Source: Applicant's Clinical Study Report 009, page 89, Figure 9

Effects of Lemborexant on Other Drugs

- Induction Effect of Lemborexant on Probe CYP3A Substrate

Midazolam:

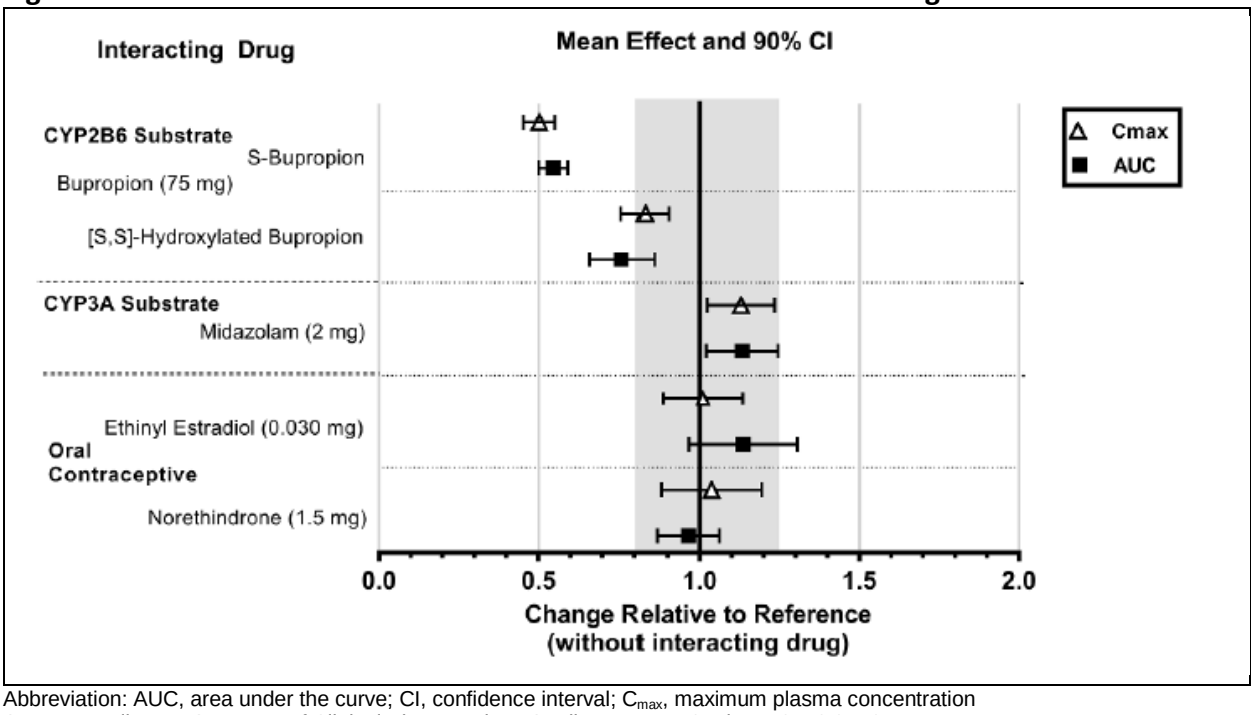
The effects of steady-state dosing of 10 mg lemborexant on the PK of midazolam (a CYP3A substrate) activity was determined in Study 004. The patients received midazolam (2 mg) and bupropion (75 mg) on Day 1 under fasting conditions. After 7 days washout, the patients received consecutively dosing of 10 mg lemborexant from Day 8 to Day 20 and a single dose of midazolam (2 mg) plus bupropion (75 mg) on Day 17 under fasting conditions. PK samples of midazolam and bupropion were measured up to 96 hours. Since midazolam (a sensitive CYP3A substrate) and bupropion (a sensitive CYP2D6 substrate) undergo different routes of elimination via different CYP enzymes, it is acceptable that midazolam and bupropion were assessed together in the same DDI study. The results show that the activity of hepatic CYP3A

was not altered by multiple doses of lemborexant. No change was observed for the C_{max} and $AUC_{0\text{-}inf}$ values for midazolam (Figure 10). Thus, dose adjustment for midazolam or any other CYP3A substrate when coadministered with lemborexant is not required.

- Induction Effect of Lemborexant on Probe CYP2B6 Substrate

Bupropion:
The effects of steady-state dosing of 10 mg lemborexant on the PK of bupropion (a CYP2B6 substrate) activity was determined in Study 004. PK samples of S-bupropion and [S, S]-hydroxylated (metabolite of bupropion) were measured up to 96 hours post-dose. The results showed that the geometric mean C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for S-bupropion decreased by approximately 50%, 45%, and 45%, respectively; while the geometric mean C_{max} and $AUC_{0\text{-}t}$ for [S, S]-hydroxybupropion decreased by approximately 17% and 25%, respectively, when coadministered with multiple doses of lemborexant as compared with bupropion alone (Figure 10). The Applicant proposed that lemborexant can be coadministered with CYP2B6 substrate. Bupropion is a racemic mixture. It is extensively metabolized in the liver via three different routes into active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. *In vitro* findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of other active metabolites. Hydroxybupropion is approximately one-half potent as bupropion for antidepressant activity, and the C_{max} and AUC are approximately 10- and 17-fold higher than the parent drug. Considering the relative activity and systemic exposure of hydroxybupropion as compared to bupropion, the Applicant proposed that less than 25% decrease in [S, S]-hydroxybupropion exposure is not considered clinically significant, and thus no dose adjustment is recommended for bupropion or other CYP2B6 substrates when coadministered with lemborexant.

Figure 10: Effects of Lemborexant on the Pharmacokinetics Other Drugs



Abbreviation: AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration
Source: Applicant's Summary of Clinical Pharmacology Studies, page 110, Figure 2.7.2.3.4-2.

Upon reviewing the Applicant's justification, the Division determined that bupropion is a better moiety that represent the change of CYP2B6 activity when coadministered with lemborexant (a CYP2B6 inducer), which are elucidated in the following key questions:

1) Which moiety (bupropion or hydroxybupropion) better represent the change of CYP2B6 activity when coadministered with CYP2B6 inhibitors or inducers?

- Hydroxybupropion is a better moiety that reflects CYP2B6 activity when coadministered with CYP2B6 inhibitors.

Since there are more than one metabolism pathways for bupropion and CYP2B6 is only involved in the formation of hydroxybupropion, the exposure change of hydroxybupropion is more sensitively associated with CYP2B6 activity as compared to the parent drug. For example, clinical DDI study of bupropion with ticlopidine [19] demonstrated that hydroxybupropion AUC was more sensitively changed (84% decrease) in the presence of CYP2B6 inhibitor as compared to bupropion (1.9-fold increase).

- Bupropion is a better moiety that reflects CYP2B6 activity when coadministered with CYP2B6 inducers.

In the presence of CYP2B6 inducer(s), both formation and elimination rates for hydroxybupropion are changed. On the one hand, hydroxybupropion is formed more rapidly due to a quicker metabolism rate of bupropion when concomitant use with CYP2B6 inducers. On the other hand, hydroxybupropion may also be more rapidly metabolized by UGTs. UGTs are regulated by Pregnane X receptor (PXR), and CYP2B6 is regulated by constitutive

active/androstane receptor (CAR). It is known that PXR cross-talks to CAR, and thus CYP2B6 inducers may also induce UGTs. Since both formation and elimination rates for hydroxybupropion may increase in the presence of CYP2B6 inducers, the exposure change of hydroxybupropion no longer reliably predicts the change of CYP2B6 activity, whereas bupropion is a better moiety in this situation.

Since bupropion is a better moiety that reflects CYP2B6 activity when coadministered with inducers, an observed 45% to 50% decrease in bupropion exposure suggests that dose adjustment for CYP2B6 substrates is necessary when coadministered with lemborexant.

2) Whether the exposure of S-isomer of bupropion and hydroxybupropion could represent the exposure changes for bupropion and hydroxybupropion, respectively?

The Applicant only measured the plasma concentrations of S-bupropion and [S, S]-hydroxybupropion, while the concentrations for R-bupropion and [R, R]-hydroxybupropion are not determined. Thus, it is unknown whether the percentage decrease in racemic bupropion exposure is similar to that observed for S-bupropion when coadministered lemborexant.

Two clinical studies that reported both enantiomers and racemic bupropion concentrations when coadministered with rifampin and ritonavir provide supporting evidence that the percentage change of racemic bupropion is similar to S-bupropion when coadministered with CYP2B6 inducers ([20]; [21]). The results showed that S-bupropion had roughly similar magnitude of exposure decrease as racemic bupropion and R-bupropion. Thus, it is reasonable to assume that racemic bupropion AUC decreased at similar percentage (~45%) as those observed for S-bupropion when coadministered with lemborexant.

3) What are the dose adjustment recommendations for known CYP2B6 substrates?

There are limited number of approved drugs identified as CYP2B6 substrates, and the dose-adjustment recommendations for each drug are discussed as below:

1. Bupropion: bupropion has two indications, antidepressant and smoking cessation. The mechanism of actions of bupropion for these two indications are very complicated that involving binding to multiple receptors (e.g., nicotinic receptor, noradrenergic and dopaminergic transporters) by both enantiomers of patient drug and metabolites. In addition, the enantiomers of bupropion and hydroxybupropion were reported to have different pharmacological activities towards different receptors [22]. Thus, it is not clear as to which moieties account for the pharmacological activity and efficacy for bupropion.

   Since both parent drug and active metabolite of bupropion showed decreased exposure when coadministered with lemborexant, dose increasement for bupropion may be warranted. According to the bupropion label, the dose of bupropion is titrated based on clinical responses. Thus, this dose titration scheme based on clinical responses is considered appropriate when coadministered with lemborexant, which may overcome

uncertainties in clinical practice as the exposure changes are different for parent drug and metabolites.

2. Methadone: Methadone is known to be metabolized by multiple CYP enzymes including CYP2B6. A recent study suggested that CYP2B6 may play a major role in the metabolism of S-methadone [23]. According to methadone drug label, we recommend monitoring signs or symptoms of opioid withdrawal in patients using methadone, and may consider increasing the dose of methadone when coadministered with lemborexant as needed.

3. Efavirenz: Efavirenz is mainly metabolized by CYP3A and CYP2B6 in the liver, and at the same time efavirenz is an auto-inducer for CYP3A and CYP2B6. As a result, the effects of other inducers on the steady-state efavirenz exposure may be smaller compared to that observed following a single-dose of efavirenz, because CYP2B6 and CYP3A4 levels have already been elevated to some extent by efavirenz after multiple doses. For example, rifampin (a strong CYP3A and moderate CYP2B6 inducer) is reported to have limited impact on the exposure of efavirenz (18% to 22% decrease) at steady-state ([24]; [25]). Therefore, lemborexant is expected to have limited induction effect on efavirenz following multiple doses, and dose-adjustment for efavirenz is not warranted.

4. Esketamine: Esketamine is formulated as a nasal spray, and it is expected that nasal spray would have a less significant first-pass effect as compared to oral formulations. Esketamine is mainly metabolized to noresketamine via CYP2B6 and CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Clinical study showed that a strong CYP3A and moderate CYP2B6 inducer rifampin decrease the esketamine exposure (e.g., C_{max} and $AUC_{0\text{-}inf}$) by less than 31%. It is expected that the exposure changes of esketamine when coadministered with lemborexant would be smaller than that observed when coadministered with a more potent inducer such as rifampin, and thus dose adjustment for esketamine is not warranted.

Based on the discussions above, we recommend the following language for lemborexant when coadministered with CYP2B6 substrates:

- The dose of bupropion may be increased when coadministered with lemborexant. Patients receiving lemborexant and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
- Coadministration of methadone with lemborexant could result in decrease in the AUC of methadone, possibly requiring a proportional dosage increase.
- No dose adjustment is recommended for efavirenz and esketamine when coadministered with lemborexant.

- Drug interaction between lemborexant and oral contraceptives

The effects of multiple doses (10 days) of 10 mg lemborexant on the PK of oral contraceptive Loestrin (norethindrone (NE) 1.5 mg/ ethinyl estradiol (EE) 0.03 mg) was determined in Study 012. The female patients received Loestrin on Day 1 under fasting conditions. After washout,

the patients received consecutively dosing of 10 mg lemborexant from Day 5 to Day 18 and a single dose of Loestrin on Day 15 under fasting conditions. PK samples of lemborexant and its metabolites (M4, M9, and M10), EE, and NE were measured up to 96 hours post-dose. The results show that lemborexant, M4, M9, and M10 exposure (based on C_{min}, C_{max}, and AUC_{0-24}) was similar when lemborexant was administered alone and with Loestrin. In addition, mean plasma concentrations (based on C_{max}, AUC_{0-t} and AUC_{0-inf}) of EE and NE were similar when Loestrin was administered alone and with lemborexant (Figure 7 and Figure 10). Thus, dose adjustment for oral contraceptive of Loestrin is not required when coadministered with lemborexant.

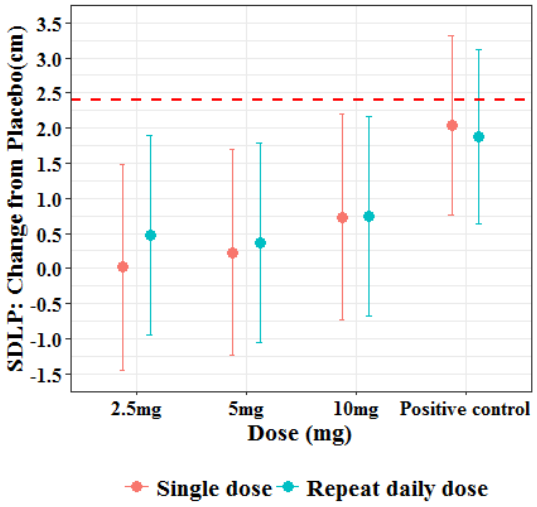
6.3.2.4. Does Lemborexant Have Potential to Impact the Next-Day Driving Performance?

The next-day driving performance of healthy adults (21 to 64 years) and elderly subjects (≥65 years) following a single dose and multiple doses of lemborexant at bedtime was evaluated in Study 106. Subjects were randomized to 1 of 12 sequences in an incomplete block design, comprising 4 treatment periods with a minimum 14-day washout between each period. Randomization was stratified by age group (adult: 21 to 64 years versus elderly: ≥65 years) in a 1:1 ratio and was balanced for sex per age group. Each subject received 2 of the 3 dose levels of lemborexant (2.5, 5 or 10 mg), zopiclone (7.5 mg, positive control) and placebo (negative control) for 8 consecutive nights.

The driving performance was assessed in the morning following the first (Day 2) and last doses (Day 9) of the treatments. Blood concentrations of lemborexant, its metabolites (M4, M9, and M10), and S-zopiclone were measured predose on Day 1 of treatment periods 2, 3, and 4, predose on Day 8, and after each driving assessment. The primary endpoint is the standard deviation of the lateral position (SDLP) during an on-road driving test in the morning on Day 2 and Day 9 following lemborexant dosing compared to placebo.

Figure 11 shows the baseline, placebo-subtracted changes in SDLP on the morning of Day 2 (single dose on Day 1) and Day 9 (repeat doses for 8 days). From Day 2 to Day 9, the change in the mean (SD) SDLP was small for all the lemborexant groups (2.5, 5 and 10 mg). The 95% confidence intervals of SDLP change in lemborexant groups (2.5, 5 and 10 mg) are below 2.4 cm (associated with blood alcohol limit of 0.5 g/L) indicating that the given doses of lemborexant did not result in impairment on the driving test compared to placebo. No subjects in lemborexant treatment group discontinued from the driving study. It is reported that risk of motor vehicle crash increases 4-fold at 0.8 g/L alcohol limit, which produces an SDLP change of 4.4 cm compared to placebo. Notably, 2 out of 32 subjects had SDLP > 4.4 cm (associated with blood alcohol limit of 0.8 g/L) in 10 mg lemborexant group, indicating the presence of inter-subject variability in the driving test. Therefore, there is a potential for next-day residual effects in some patients taking 10 mg lemborexant.

Figure 11: Placebo Subtracted Changes in SDLP on the Morning of Day 2 (Single Dose on Day 1) and Day 9 (Repeat Doses for 8 Days)

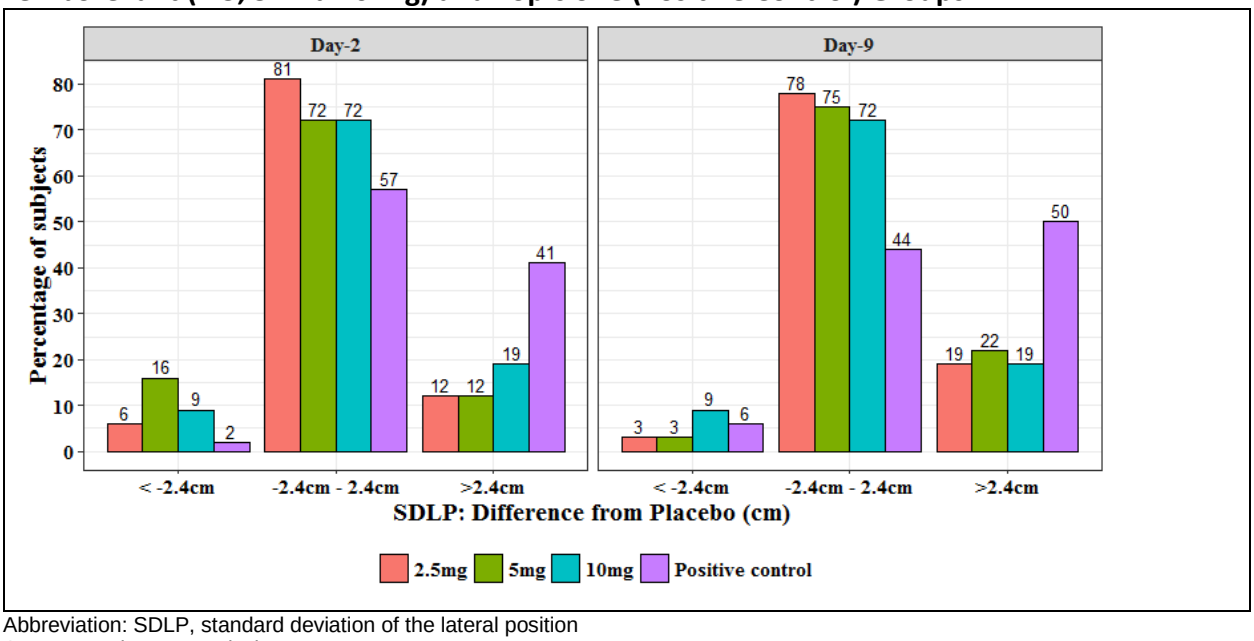


*The reference lines at 2.4 and 4.4 cm refer to SDLP changes at alcohol limits of 0.5 g/L and 0.8 g/L.

Abbreviation: SDLP, standard deviation of the lateral position
Source: Reviewer's analysis based on data obtained from clinical study report 106, Page 96, Table 11

Figure 12 shows the distribution of changes in SDLP on Day 2 and Day 9 across doses. No clear relationship between the dose and proportion of patients with SDLP > 2.4 cm can be observed on Day 2 and Day 9.

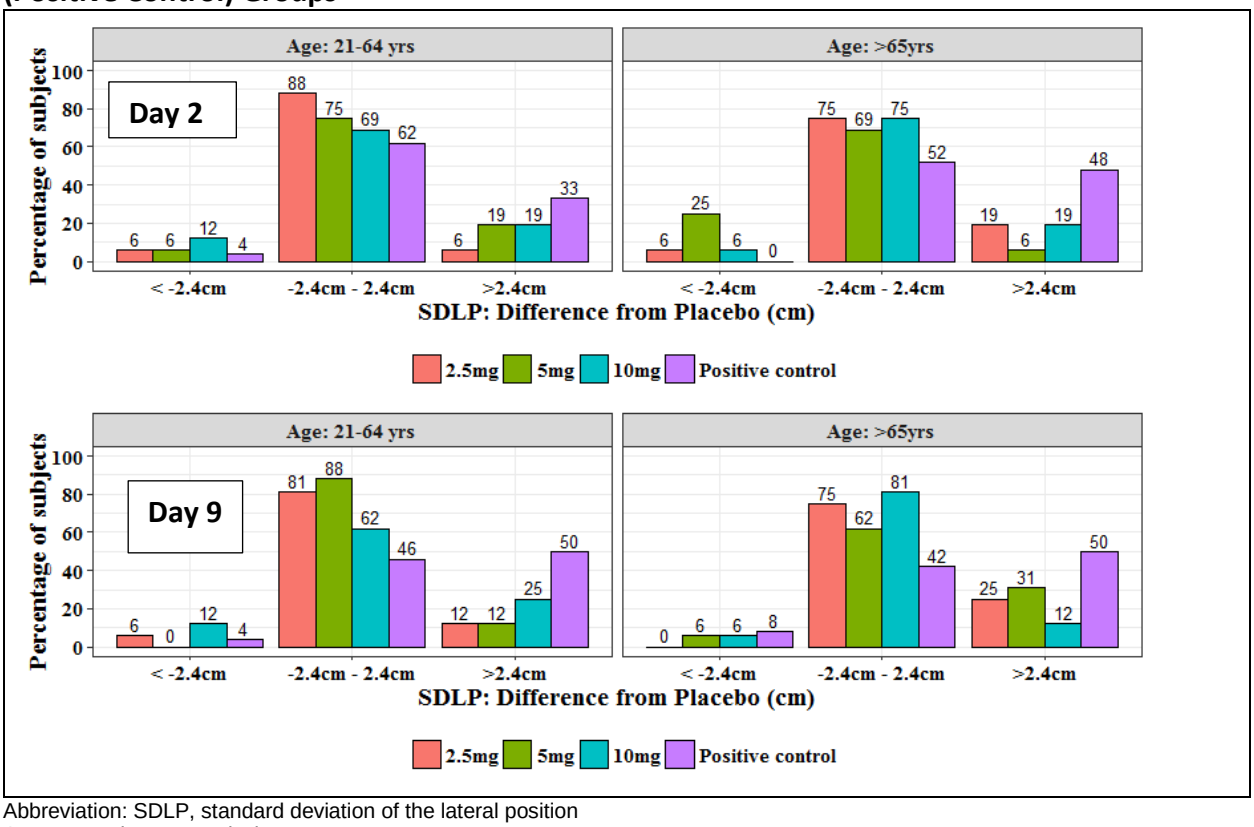
Figure 12: Proportion of Subjects With SDLP Changes (<-2.4 Cm, -2.4 To 2.4 Cm, >2.4cm) in Lemborexant (2.5, 5 And 10 Mg) and Zopiclone (Positive Control) Groups



Abbreviation: SDLP, standard deviation of the lateral position
Source: Reviewer's analysis

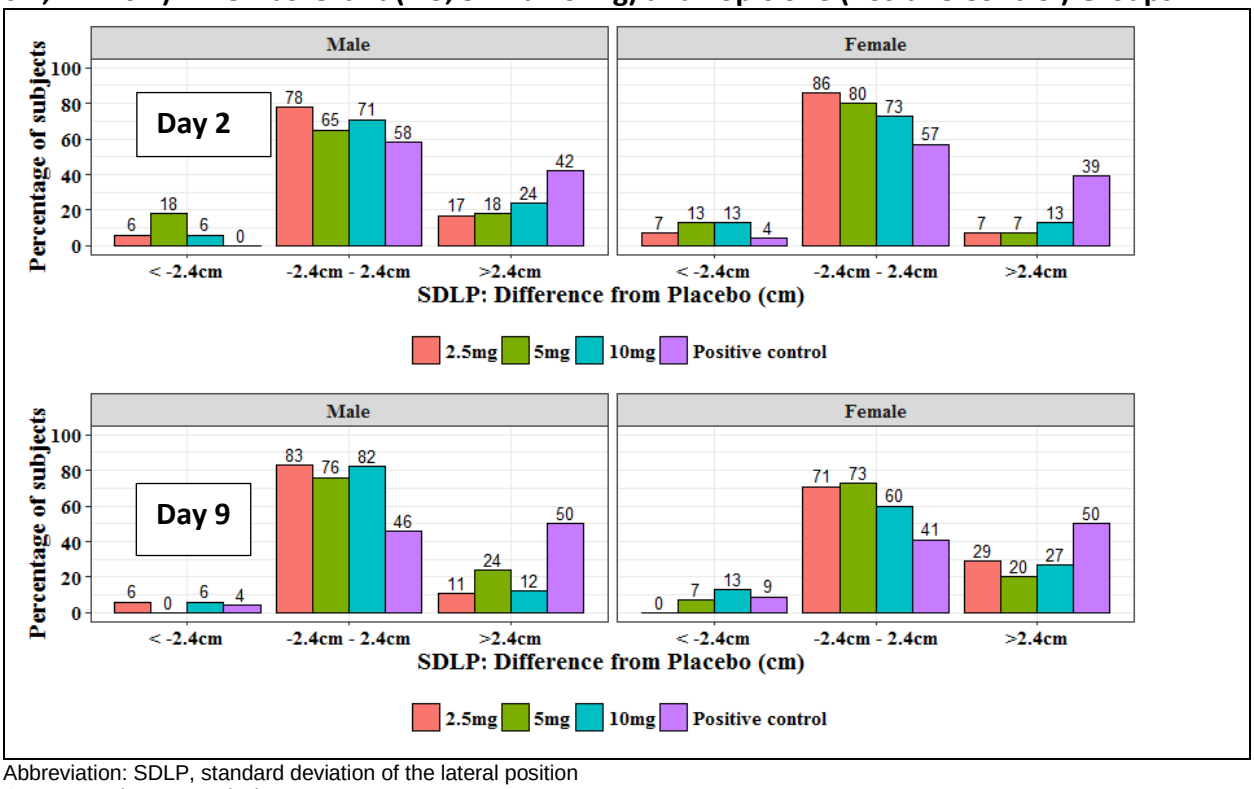
No relationship between the dose and proportion of subjects with SDLP>2.4cm by age can be observed on Day 2 and Day 9 in Figure 13. Similarly, no relationship between the dose and proportion of subjects with SDLP>2.4cm in male and female subjects can be observed on Day 2 and Day 9 in Figure 14.

Figure 13: Proportion of Non-Elderly (21-64 Yrs) and Elderly (>65 Yrs) Subjects With SDLP Changes (<-2.4 Cm, -2.4 To 2.4 Cm, >2.4cm) in Lemborexant (2.5, 5 And 10 Mg) and Zopiclone (Positive Control) Groups



Abbreviation: SDLP, standard deviation of the lateral position
Source: Reviewer's analysis

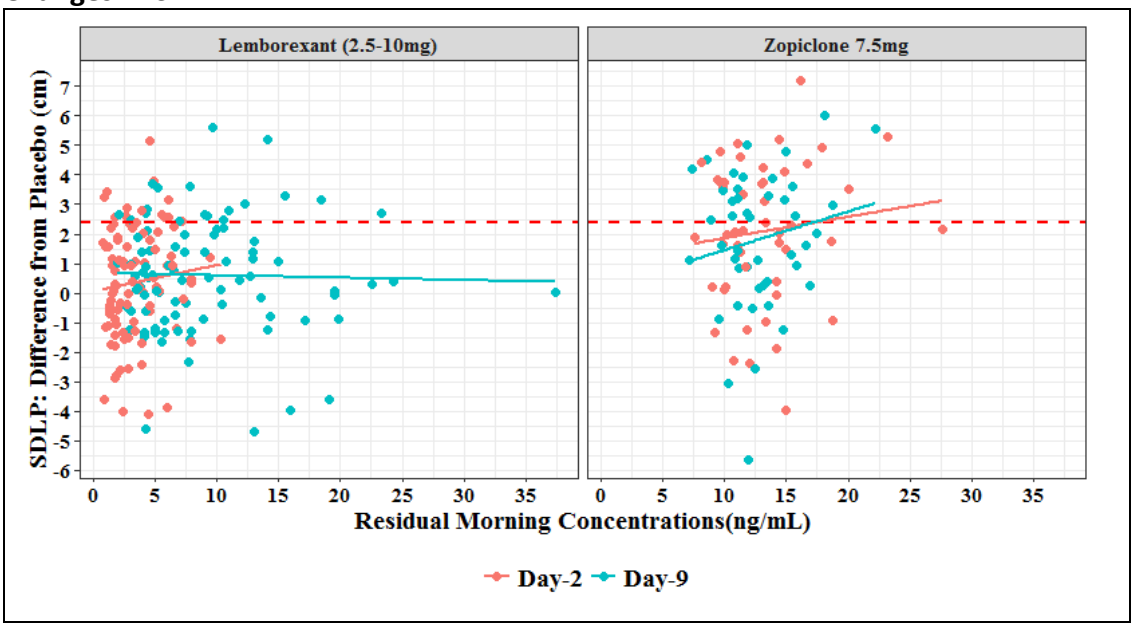
Figure 14: Proportion of Male and Female Subjects With SDLP Changes (<-2.4 cm, -2.4 To 2.4 cm, >2.4 cm) in Lemborexant (2.5, 5 And 10 Mg) and Zopiclone (Positive Control) Groups



Abbreviation: SDLP, standard deviation of the lateral position
Source: Reviewer's analysis

Figure 15 shows the findings of linear regression analysis of the relationship between the next-day residual concentrations of lemborexant and placebo-corrected SDLP changes. The 95% CI of the slope includes zero indicating a lack of statistically significant relationship.

Figure 15: Relationship Between Next-Day Residual Concentrations and Placebo-Corrected Changes In SDLP



Abbreviation: SDLP, standard deviation of the lateral position
Note: Shown are data from lemborexant and zopiclone groups
Source: Reviewer's analysis

Lemborexant pharmacokinetics were reported to increase in subjects with hepatic and renal impairment, with alcohol, and when coadministered with CYP3A inhibitors. However, according to the dosing individualization, lemborexant is recommended either not to be used (i.e., severe hepatic impairment, strong and moderate CYP3A inhibitors, and alcohol) or capping at 5 mg without a titration option (e.g., weak CYP3A inhibitor) when there is a significant exposure increase. As a result, lemborexant exposure is not expected to increase by more than 1.5-fold when the patients following the individualized dosing recommendations for each of these intrinsic and extrinsic scenarios.

6.3.2.5. Is the To-Be-Marketed Formulation the Same as the Clinical Trial Formulation, and if Not, Are There Bioequivalence Data To Support the To-Be-Marketed Formulation?

Yes. The to-be-marketed formulation was used in the pivotal efficacy and safety studies and key clinical pharmacology studies.

The clinical program for lemborexant used two formulations, a capsule formation that was initially being used in the single-ascending dose and multiple-ascending dose studies and a tablet formulation that was used in later clinical studies. The relative bioavailability of capsule and tablet formation was assessed in Study 005 in healthy adult subjects. The results show that the bioavailability of the tablet and capsule formulations was similar. Differences between tablet and capsule formulations for $AUC_{0\text{-}inf}$ were each less than 13%, and the differences between the tablet and capsule formulations in C_{max} across all dose levels were each less than 16%.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Studies submitted by the Applicant under NDA 212028 and used for the efficacy and safety review are listed in Table 26. These studies were completed in North America, Europe, Asia, and Oceania.

Table 26: Listing of Clinical Trials Relevant to NDA 212028

Controlled Studies to Support Efficacy and Safety								
Trial Identity	**NCT no.**	**Trial Design**	**Regimen (PO Nightly)**	**Key Study Endpoints**	**Treatment Duration**	**No. of patients enrolled**	**Study Population**	**No. of Centers and Countries**
E2006-G000-303 (Core) Period 1	0295820	MC, R, DB, PC, parallel-group study 2-week PBO run-in	LEM5 LEM10 PBO	Primary endpoint: Mean change from Study Baseline in SOL at Month 6. Secondary endpoints: Mean change from Baseline in sSE at Month 6. Mean change from Study Baseline in sWASO at Month 6.	Period 1: 6 months	2060 enrolled (971 subjects randomized) LEM5 (n=323); LEM10(n=323); PBO (n=325); 27.6% >= 65 yo 68.2% female 71.5% white	Age >= 18 yo Otherwise Healthy adults with DSM5 insomnia disorder (history and current); No current other sleep disorders; ISI ≥15 BDI-II score ≤19 and BAI score ≤15 at Screening	119 Sites 40 US 24 JP 9 KR, 7 DE 7 PL 6 FI 5 RO 5 NZ 5 ES 4 CA 4 IT, 2 TW 1 MX
E2006-G000-303-EXT, Period 2		PBO from Period 1 re-randomized LEM5 or LEM10	LEM5 LEM10 PBO	Additional Secondary: Persistence, sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to PBO (sSOL, sWASO) at Month 6 and Month 12	Period 2: 6 months	PBO to LEM5 (n=133) PBO to LEM10 (n=125) LEM5 to LEM5 (n=251) LEM10toLEM10 (n=226)	Otherwise Healthy Adults with DSM5 insomnia disorder Age >=55 years old (female) Age >=65 years old (male) Range 55-88 45% Elderly	

E2006-G000-304 Phase 3 Pivotal	02783729	MC, R, DB, PC, AC parallel-group study	PBO; LEM5; LEM10; ZOL (ZOL ER 6.25 mg) PBO	Primary endpoint: Change from baseline of mean LPS Secondary endpoints: mean SE and mean WASO on Days 29/30 of LEM10 and LEM5 compared to PBO Change from baseline of mean WASO2H on Days 29/30 of LEM10 and LEM5 compared to ZOL	30 days treatment/ minimum 14 days follow up	3537 enrolled subjects (1006 randomized) LEM5 (n=266) LEM10 (n=269) ZOL (n=263) PBO (n=208)	Males ≥65 years Females ≥55 years DSM5 insomnia disorder history and current; No current other sleep disorders ISI ≥13 BDI-II score ≤19 at Screening BAI score ≤15 at Screening	88 sites: 54 US 9 ES 8 DE 6 CA 3 UK 4 IT 4 FR
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
Trial Identity	**NCT no.**	**Trial Design**	**Regimen (PO Nightly)**	**Primary Study Endpoint(s)**	**Treatment Duration**	**No. of patients enrolled**	**Study Population**	**No. of Centers and Countries**
E2006-A001-001 (Part B)	01463098	R, DB, PC, parallel group Single Dose Study	LEM2.5 LEM10 LEM25 PBO ZOL	Safety Tolerability PK PD	4 Days	LEM2.5 (n=13) LEM10 (n=10) LEM25 (n=12) PBO (n=12) ZOL (n=11)	Males or females ≥18 years Insomnia disorder (DSM-IV-TR), History of insomnia symptoms (sSOL, sWASO) ISI >15 BDI-II score ≤19 at Screening BAI score ≤15 at Screening	2 US Sites

E2006-A001-008	02089412	Open-label, crossover, food-effect study of LEM10 in healthy subjects	LEM10	AUC, Cmax, tmax	15 Days	LEM10 (n=24)	Males or females 18 to 55 years	1 US Site
E2006-A001-009	03483636	DC, PC, crossover study of ethanol ±LEM10	LEM10 + alcohol	CFB body sway, Cognitive performance for ethanol ±LEM10	1 day each	LEM10 (n=32)	Males or females 19 to 55 years, Current alcohol users	1 Canadian site
E2006-A001-012	03451110	Open-label, DDI study of Loestrin®, famotidine, and fluconazole on PK of LEM10 and M4, M9, M10	LEM10 + drug	Cmax, AUC, t1/2, DDI	15 Days	n=50	Females ≥18 and ≤44 years at (Part 1) Males and females, ≥18 to ≤55 years (Part 2 and 3)	1 US site
E2006-A001-102	03471871	DB, PC, crossover study of respiratory safety of LEM10	LEM10 PBO	Mean Peripheral Oxygen Saturation (SpO2) During Total Sleep Time (TST) Day 1, Apnea-Hypopnea Index (AHI) on Day 8	8 days	LEM10 LEM25 PBO (n=78)	Adult and elderly subjects with mild OSA Males or females ≥18 to ≤90 Years SpO2 ≥94%, OSA,	8 US sites
E2006-A001-103	03158025	DB, PC, AC crossover, abuse potential study	PBO LEM10 LEM20 LEM30 ZOL30 SUV40	Mean peak Maximum Effect (Emax) score for Drug Liking on a Visual Analog Scale	1 day each	n=39	Males or females 18 to 55 years, recreational sedative abusers	1 Site Canada

E2006-A001-104	03440424	Open-label, parallel-group study of the PK of LEM10 moderate hepatic impairment and healthy controls	LEM10	Cmax, AUC	14 Days	LEM10 (n=24)	Males or females 18 to 79 years with stable hepatic impairment (Child-Pugh classification A or B) and healthy matched control subjects	2 US Sites
E2006-A001-105	03443063	Open-label, parallel-group study of the PK of LEM10 in subjects with severe renal impairment and healthy controls	LEM10	Cmax, AUC	8 days	LEM10 (n=16)	Males or females 18 to 79 years with stable severe renal impairment and healthy matched control subjects	2 US Sites
E2006-E044-106)	02583451	R, DB, PC, AC, 4-Period Crossover Study to Evaluate the Effect of LEM v PBO on Driving	LEM2.5 LEM5 LEM10 PBO ZOL	Change of standard deviation of lateral position (SDLP) during an on-road driving test	72 days	n=4	Males or females ≥21 years At least 3 years of experience driving at least 3000 km per year	1 NL Site
E2006-A001-107	02350309	DB, PC, crossover study of morning sleep propensity	LEM5 LEM10 PBO Flurazepam, 30 mg	Primary: mean CFB in average SOL from MSLT	2 days each treatment	n=79	Males and females ≥18 years DSM5 Insomnia disorder ISI score ≥15	2 US Sites

E2006-A001-108	03008447	R, DB, PC, AC, 4 Period Crossover Study LEM, PBO, ZOL Postural Stability, Awakening Threshold, and Cognitive Performance	LEM5 LEM10 PBO ZOL	Primary: Change from time-matched baseline in postural stability for LEM5 and LEM10 vs ZOL at 4 hours postdose; Magnitude of body sway 4 hours after LEM	Single dose	n=63	Males ≥65 years Females ≥55 years No current sleep disorder	4 US Sites
E2006-G000 201 Phase 2 Study	01995838	MC, R, DB, PC parallel group, Bayesian Adaptive Randomization Design, dose-response study	LEM1 LEM2.5 LEM5 LEM10 LEM15 LEM25 PBO	Primary: Change from mean SE at Baseline to mean SE after dosing on Days 14/15. Change from mean LPS at Baseline to mean LPS after dosing on Days 14/15. Change from mean WASO at Baseline to mean WASO after dosing on Days 14/15.	14 days	LEM (n=235) PBO (n=56)	Males or females ≥18 years Insomnia disorder (DSM-IV-TR) History of insomnia symptoms (sSOL, sWASO) ISI >15 BDI-II score: ≤19 at Screening BAI score ≤15 at Screening	23 US Sites

E2006-G000-202 Core and Exten-sion	03001557	MC, R, DB, PC Parallel-Group Study With Open-Label Extension Phase of the Efficacy and Safety of LEM	LEM2.5 LEM5 LEM10 LEM15 PBO	CFB on numerous sleep measures	29 Days	LEM2.5 (n=12) LEM5 (n=13) LEM10 (n=13) LEM15 (n=12) PBO (n=12) Extension LEM (n=25)	Males or females age 60-90 Alzheimer's Dementia MMSE 10 to 26 at Screening Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (DSM-5 and ICD-10); Frequency of complaint of sleep and wake fragmentation ≥3 days per week; Duration of complaint of sleep and wake fragmentation ≥3 months	57 sites 47 US 1 EU 9 JP

Abbreviations: AC, active controlled; ADME, absorption, distribution, metabolism, and excretion; BAI, Beck Anxiety Index; BDI-II; Beck Depression Inventory – II; CA, Canada; DB, double blind; DDI, drug–drug interaction; DE, Germany; DSM Diagnostic and Statistical Manual of Mental Disorders; ER, Extended Release; ES,Spain; EU, Europe; FI, Finland; FR, France; ICD, International Classification of Diseases; ISI, Insomnia Severity Index; IT, Italy; JP, Japan; KR, South Korea; LEM5, lemborexant 5 mg by mouth at night; LEM10, lemborexant 10 mg by mouth at night; LPS, latency to persistence sleep; MAD, multiple ascending dose; MC, multicenter; MMSE, Mini Mental State Examination; MX, Mexico; NCT, National Clinical Trial; NZ, New Zealand; OSA, obstructive sleep apnea; PBO, placebo; PC, placebo controlled; PD, pharmacodynamic; PK, pharmacokinetics; PL, Poland; R, randomized; RO, Romania; SAD, single ascending dose; SE, standard error; sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sWASO, subjective wake after sleep onset; UK, United Kingdom; US, United States; TW, Taiwan; ZOL, zolpidem
Source: Modified from Sponsor's Table of lemborexant Clinical Studies, 5.3.5.3 Pages 19-35

7.2. Review Strategy

The Applicant submitted 20 studies that were conducted as part of the drug development program for lemborexant. The review team considered the potential contribution of each submitted study to the overall approach to the efficacy and safety. Table 26 above tabulates the studies included in the review of efficacy and safety. A complete table of submitted studies can be found in Section 8.2.2, Table 57.

Study 303-Core and Study 304 were chosen as the primary studies for both safety and efficacy because they were large, randomized, double-blind, placebo-controlled studies conducted in the population of interest (insomnia disorder) and used the Applicant's proposed doses of lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10). Study 303 also included a parallel-group extension study (Study 303-EXT) which re-randomize subjects in the placebo group into a treatment arm with lemborexant. Results from the 12-month combined (Study 303-Core and Study 303-EXT) were considered for the safety review.

There are two phase 2 studies in the lemborexant drug development program. The Applicant's Study 201 was not considered to be a pivotal study supporting the efficacy or safety of lemborexant. We considered this study to be exploratory in nature, because it used a Bayesian adaptive statistical design with a primary endpoint which was a utility function combining both sleep efficiency (efficacy) and next-day sleepiness (safety). This combination primary endpoint made interpretation of findings less straightforward compared to the primary phase 3 studies (303 and 304) in the lemborexant drug development program. Study 202 is an ongoing study for the development of irregular sleep-wake rhythm disorder (ISWRD) in Alzheimer's disease. Because the population was unrelated to the indication for lemborexant, this study was not considered in efficacy and was only considered in safety when considering rare events.

The remaining studies were phase 1 studies designed to examine pharmacodynamics (PD), pharmacokinetics (PK), and the safety and tolerability of lemborexant in subjects with insomnia, other sleep disorders, and in special safety populations and healthy volunteers. Phase 1 studies were considered for safety, when relevant.

We reviewed the Applicant's analyses for the efficacy and safety review. The FDA statistical team and clinical review team conducted independent analyses of the Applicant's submitted data to confirm or supplement the Applicant's analyses, as deemed appropriate.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

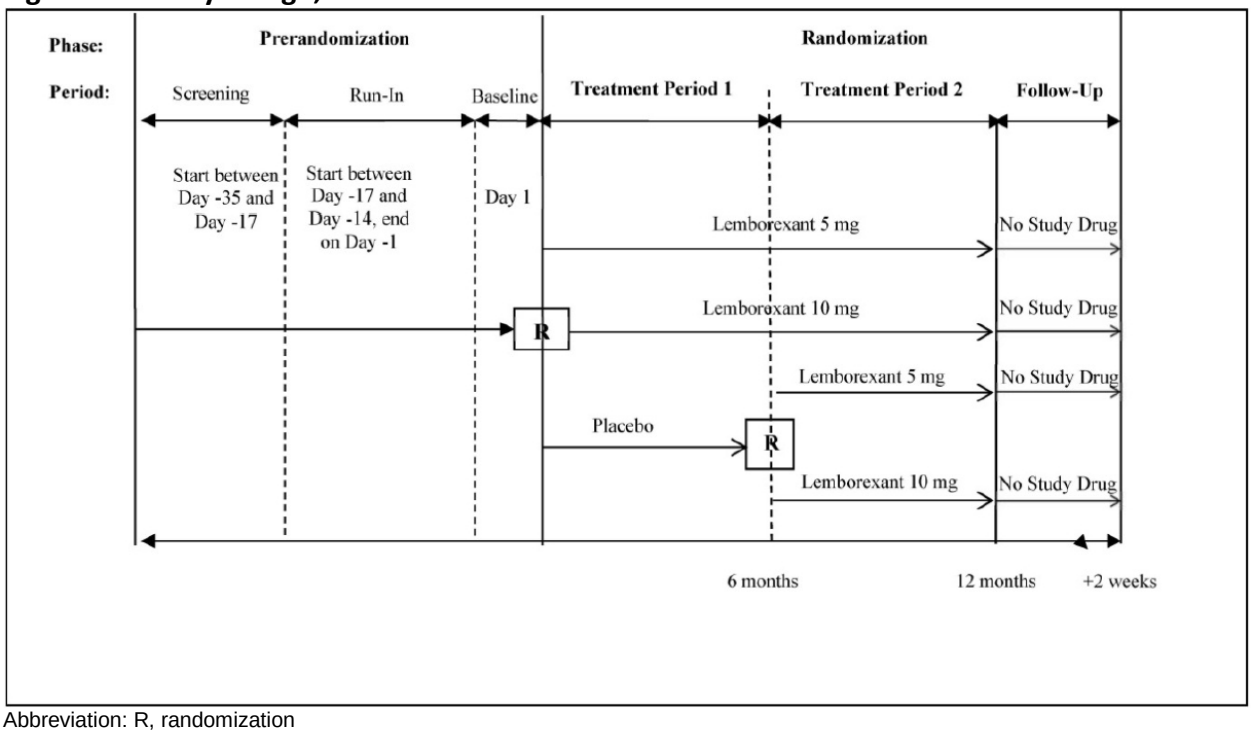
8.1.1. E2006-G000-303

8.1.1.1. Trial Design for E2006-G000-303

Study design: Study 303 was a 12-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of two dose levels of lemborexant (5 or 10 mg nightly) in approximately 900 male or female subjects with insomnia disorder. Approximately 40% of the population was to be age 65 years or older. The study had two phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase comprised three periods that lasted up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Screening period began no more than 35 days before the subject was randomized and consisted of 2 visits. During the Run-in period, subjects took placebo each night immediately before bedtime. The run-in period lasted approximately 14 nights and a maximum of 17 nights. On Day 1, the Run-in period ended and the Baseline period took place. Subjects returned to the clinic for this visit (Visit 3). Subjects who completed the Baseline period and continued to meet the eligibility criteria were randomized and began treatment in the randomized phase. The Randomization Phase comprised a 6-month, placebo-controlled treatment period (Period 1, referred to as 303-Core). During this phase, patients were randomized in 1:1:1 ratio to placebo (PBO), LEM5, and LEM10 based on two stratification factors: country and age group (<65 years old; ≥65 years old). During the next 6 months (Period 2, referred to as 303-EXT), subjects received only active treatment. Specifically, the subjects on LEM5 were continued on LEM5. The subjects on LEM10 were continued on LEM10. The subjects on placebo (PBO) were re-randomized to either LEM5 or LEM10. Subjects were informed that they would all receive PBO at some point during the study (including placebo run-in) and that all would receive active treatment for at least 6 months. They were not informed of either the timing of these periods or the timing of the second randomization. A 2-week Follow-Up Period then took place, followed by an End of Study (EOS) Visit. The study design is presented in Figure 16. Site locations included North America, Europe, Asia, and Oceania.

Clinical Reviewer Comments*: The overall design was consistent with previously agreed-upon discussions with the FDA. Although subjects were blinded to the re-randomization in Study 303-EXT, the approach has limitations for the efficacy review, because the placebo-controlled data for Study 303 is limited to only the first-six months.*

Figure 16: Study Design, E2006-G000-303



Abbreviation: R, randomization
Source: Applicant's Clinical Study Report for E2006-G000-303, Figure 1

Choice of Control Group: The control group consisted of subjects who met the inclusion and exclusion criteria for Study 303 and were randomized to placebo.

Diagnostic Criteria: A medical, psychiatric, and sleep history interview was conducted to determine if the subject met inclusion criteria for insomnia disorder according to DSM-5 criteria, as follows: (1) complained of dissatisfaction with nighttime sleep in the form of difficulty getting to sleep, difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep; (2) frequency of complaint ≥3 times per week; (3) duration of complaint ≥3 months; and, (4) associated with complaint of daytime impairment.

Additionally, subjects were required to have a complaint of difficulty with sleep onset, sleep maintenance, or both, captured using the Insomnia Severity Index (ISI). Detailed inclusion criteria are listed below.

Overview of Key Inclusion Criteria:

- Age 18+
- Confirmation of difficulty with sleep
    - Met DSM-5 diagnostic criteria for Insomnia Disorder
    - At Screening: History of subjective sleep onset latency (sSOL) ≥30 minutes on at least 3 nights per week in the previous 4 weeks and/or subjective wake after sleep onset (sWASO) ≥60 minutes on at least 3 nights per week in the previous 4

weeks.
    - At Screening and Study Baseline: ISI score ≥15
    - At the second Screening Visit (Visit 2a) and Baseline (Visit 3a): Confirmation of insomnia symptoms, determined from responses on the Sleep Diary completed on at least 7 consecutive mornings, such that sSOL ≥30 minutes and/or sWASO ≥60 minutes (for Screening Visit 2a: minimum 5 of 7 nights for eligibility, and for Baseline Visit 3a: minimum 3 of 7 nights).
- Confirmation of regular bedtimes and waketimes and of sufficient duration, defined as:
    - At screening, report of regular trying to sleep 7 to 9 hours, a regular bedtime, and a regular getting out of bed time
    - At first Screening Visit 1, Visit 2a, and Baseline Visit 3a: Reported regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject got out of bed for the day, between 05:00 and 10:00 and regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours.
- Willingness to not to start other treatments for insomnia during the study, including behavioral treatments.

Overview of Key Exclusion Criteria:

- Significant current medical diseases, positive for HIV or viral hepatitis, prolonged QTcF (>450 ms), planned surgery, comorbid nocturia, and other clinically significant diseases that might interfere with study assessment
- Current sleep-related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, symptoms of narcolepsy, PSG in the past year with elevated hypopnea index, and history of complex sleep behavior
- Exclusionary scores on the Sleep Disorders Screening Battery [SDSB] as follows: the Epworth Sleepiness Scale (ESS) >15, the STOPBang (screens for obstructive sleep apnea) ≥5, and the International Restless Legs Scale (IRLS) ≥16
- Mild Beck Depression Inventory – II (BDI-II) score >19 at screening. Mild Beck Anxiety Inventory (BAI) score >15 at screening, suicidal ideation, any suicidal behavior in the past 10 years, and other clinically significant disorders or diseases that might interfere with study assessments
- Nap more than 3 times per week, frequent nocturia, excess caffeine use, drug or alcohol abuse/dependence, excessive alcohol consumption, recent insomnia treatment, failing suvorexant treatment deemed of appropriate dose and of adequate duration, in the opinion of the investigator

Clinical Reviewer Comments*: The inclusion criteria focused on insomnia symptoms and sleep-related behaviors and are within expectations for a insomnia drug development program. Limiting unnecessary medical exclusion criteria is considered a strength for generalizability. However, excluding subjects with moderate to severe anxiety or depressive symptoms may limit real world extrapolation because approximately 40 to 50% of adults with insomnia present with a comorbid psychiatric diagnosis, and symptoms of depression, anxiety, and cognitive changes*

are commonly reported in subjects with insomnia disorder (DSM-5, 2014). However, these limitations do not preclude granting the indication because they are consistent with study designs used in the development program of other drugs approved for the treatment of insomnia.

Dose Selection: The Applicant selected LEM5 and LEM10 after completing studies 201 and 107. In Study 201, doses ranging from 1 mg to 25 mg were selected as meeting the primary objective of balancing efficacy (change from baseline for sleep efficiency, SE) and safety (subjective sleepiness on the Karolinska Sleepiness Scale (KSS) one hour after wakening). The Applicant determined that doses of 5 mg and 10 mg balanced efficacy and safety. See Section 6.3.2.2 Figure 2 *Relationship Between Lemborexant Dose and Benefit-Risk*, which demonstrates that efficacy plateaus after 10 mg. Study 107 was completed to rule out a clinically meaningful effect on next-morning residual sleepiness for doses LEM5 and LEM10 compared to placebo. The Applicant felt the results of Study 107 confirmed that LEM5 and LEM10 were the appropriate doses for phase 3 trials. See Section 8.2.5.3, *Next Day Sleepiness and Sleep Propensity*, for additional details on Study 107.

Clinical Reviewer Comments: *The doses selected for study 303 (5 mg and 10 mg) were reasonable based on the Applicant's rationale of balancing efficacy and next-day sedation as observed in the earlier studies 201 and 107.*

Study Treatments: The subjects took LEM5, LEM10, or lemborexant-matched placebo orally in tablet form each night, immediately before the time the subject intended to try to sleep. For the Run-in Period, all subjects received 1 lemborexant-matched placebo tablet for at least 14 days between Days –17 and Day –1. During Period 1 (Day 1 through end of Month 6), all subjects received 1 tablet of the assigned drug according to their randomized treatment group. The study drug was taken immediately before the subject intended to sleep, on a schedule that was as consistent as possible. Subjects were not to eat a meal within 3 hours before taking the study drug due to the mild food effect noted in Study 008.

Assignment to Treatment for Study 301, Period 1: On Baseline Day 1, subjects were assigned to treatment groups using a computer-generated randomization strategy. Subjects were randomized to LEM5, LEM10, or PBO in 1:1:1 ratio. The groups were stratified by country and age group (<65 years old; ≥65 years old).

Period 2: At the end of Month 6 (Period 2 Baseline), subjects who received PBO during Period 1 underwent a second randomization to receive either LEM5 or LEM10 (1:1, stratified by country and age group (<65 years old; ≥65 years old) during Period 2. Subjects who received lemborexant during Period 1 continued to receive lemborexant at the same dose level during Period 2.

Blinding: During the run-in period, the research personnel were aware the drug was a placebo, but the subject was blinded to study drug (single blind). During Period 1 (303-Core) and 2 (303-

EXT), the study was double-blind (patient and all members of the research team). Subjects were informed only that all would receive PBO at some point in the study and that all would receive active drug for at least 6 months. They were not informed of the timing of the second randomization (at the end of Month 6). Randomization data was filed securely by with the Applicant or contract research organization (CRO), and accessible only to authorized persons (e.g., Eisai Global Safety) until the time of unblinding. The data safety monitoring board (DSMB) and the independent statistician had sole access to the unblinded interim safety data until the planned analysis of the data. When all subjects had completed Period 1 (Study 303-Core), all data were unblinded to the Applicant. Study sites and subjects remained blinded until Period 2 of the study was completed.

Dose Modification, Dose Discontinuation: No planned modifications of doses were made other than the re-randomization of the PBO-arm during Period 2. Therefore, no changes to dosing were made due to non-response or due to adverse events (e.g., over sedation). The randomized dose was maintained to improve interpretation of long-term outcomes on a single drug dose. This approach is reasonable for a phase 3 efficacy study of insomnia disorder treatment. However, in clinical practice, changes in dosing are routinely made in response to efficacy or adverse events. The lack of allowable dose modification is not reflective of clinical practice and may have contributed to the number of non-completers for this study.

Administrative Structure: The Applicant listed key sponsor personnel involved in the clinical conduct of the study in Section 6 of the Clinical Study Report (CSR). The study was monitored by personnel from (b) (4) Data management was performed by the Eisai Data Management group within Eisai Inc.; statistical analyses were performed by (b) (4), under the supervision of the Biostatistics group at Eisai Inc; population pharmacokinetic (PK) pharmacodynamic (PD) analyses were performed by the Modeling & Simulations group at Eisai Inc. Serious adverse event (SAE) reporting and management was handled by (b) (4) and Eisai Pharmacovigilance, and all subject serious adverse event narratives were approved and verified by Eisai Pharmacovigilance. Laboratory tests were performed at multiple sites and PK sample bioanalyses were performed by (b) (4) The Applicant used a data safety monitoring board (DSMB) to serve as an independent safety monitoring committee and performed the safety data reviews. The interim safety analyses were conducted by an independent statistician, who was working on behalf of Eisai from a contract research organization (CRO) that was independent of study conduct.

Dietary Restrictions: Subjects were not to eat a meal within three hours of taking the study drug. There were no other dietary restrictions.

Concurrent Medications: Prior medications were defined as medications that stopped before the first dose of study drug, including placebo during the Run-in Period. Concomitant medications were defined as medications that (1) started before the first dose of study drug (including placebo Run-in Period) and were continuing at the time of the first dose of study

drug, or (2) started on or after the date of the first dose of study drug (including the placebo Run-in Period) to the last dose day plus 14 days.

Classes of drugs excluded from this study included concurrent use of the following: sedating anticonvulsants, antihistamines (unless non-sedating), sedative anxiolytics, strong and moderate CYP3A inhibitors, CYP3A inducers, melatonin, muscle relaxants, stimulants, and other drugs, such as warfarin, heparin, ticlopidine, non-stimulant diet pills, systemic isotretinoin, systemic glucocorticoids and tryptophan. The full list of prohibited medications was provided by the Applicant as part of the NDA submission.

Any therapy or medication (including over-the-counter) administrated to the subject during the study was recorded on an electronic case report form (eCRF).

Rescue Medications: No other treatment was permitted for insomnia disorder and no other treatments were offered for subjects who did not respond to their assigned treatment.

Treatment Compliance, Subject Completion, Continuation, Withdrawal: Treatment compliance (in %) for each study drug was calculated as follows:

$$\frac{100 \times (\text{Total number of tablets dispensed} - \text{Total number of tablets returned or lost})}{\text{Number of tablets expected to be taken}}$$

Subjects who withdrew from the study were not replaced, regardless of the reason for withdrawal. See statistical section for handling of noncompleters.

Clinical Reviewer Comments*: Several categories of medications were prohibited as concomitant medications. However, the choices were inconsistent. For example, several categories of drugs that cause sedation or increased alertness were not excluded (e.g., sedating or alerting antidepressants, sedating antipsychotics, and "non-sedating" antihistamines). As such, subjects could be using these medications to improve sleep or increase alertness, and it would not have been prohibited at baseline or during the study. This choice could influence efficacy data, but due to randomization, the likelihood of concomitant medications should have been similar across treatment arms.*

The dosing strategies and treatment restrictions used by the Applicant do not reflect real-world clinical practices. However, the choices are consistent with other insomnia drug development programs and therefore do not preclude granting approval.

For example, the lemborexant draft label states that the recommended dosage is 5 mg and may be increased to 10 mg based on clinical response and tolerability. However, in Study 303, half of the subjects were randomized into the lower dose and were not permitted to increase to LEM10 even if efficacy was inadequate for 12 months. In real world populations, dosage titration would be considered if efficacy was present but insufficient at lower doses.

Psychoeducation or behavioral interventions applicable to insomnia were not provided to subjects at any time during the study. Rescue medications for the treatment of insomnia were not permitted. Furthermore, subjects agreed not to engage in other treatments for insomnia, including behavioral therapies. Restricting treatment was reasonable, however, because additional treatments could confound the assessment of efficacy. Notably, dropout rates were relatively low in Study 303, suggesting that subjects tolerated the restrictions on treatment.

Study Endpoints for E2006-G000-303

The primary efficacy endpoint was the mean change from baseline (CFB) of log transformed subjective sleep onset latency (sSOL) at Month 6 for LEM5 and LEM10 compared to PBO. The choice of primary endpoint for lemborexant was discussed with the FDA prior to the conduct of the study, and the FDA agreed to this single primary endpoint for Study 303. The primary endpoint was not modified during or after the study. This primary efficacy measure has been previously accepted to support the approval of another drug in the same therapeutic class (NDA 204569, suvorexant, which used primary efficacy measures of sSOL and sWASO). The time of the primary endpoint (e.g., 6 months after baseline) is longer than other insomnia disorder drug development programs (e.g., 3 months duration for suvorexant; 3 weeks for zolpidem ER).

Key secondary endpoints were defined as endpoints that were prespecified and corrected for multiplicity. For Study 303, the Applicant listed two key secondary endpoints: CFB of subjective sleep efficiency (sSE) and sWASO at Month 6 for LEM10 and LEM5 compared to placebo (see Table 27).

Additional secondary endpoints included:

- LEM5 and LEM10 compared to placebo on sSOL, sSE, sWASO, and sTST for the first 7 nights after treatment, after 1 month of treatment, 3 months of treatment, and 6 months of treatment.
- Efficacy of LEM5 or LEM10 compared to placebo on the Insomnia Severity Index (ISI) after 6 months.
    - The **Insomnia Severity Index (ISI)** is a 7-item, self-report questionnaire assessing the nature, severity, and impact of insomnia [27]. The dimensions evaluated were: severity of sleep onset; sleep maintenance; early morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning; noticeability of the sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale was used to rate each item (from 0=no problem to 4=very severe problem) yielding a total score from 0 to 28. The ISI was measured as mean change from baseline to EOS.
    - **Patient Global Impression – Insomnia (PGI-I):** The PGI-I, a self-report 4 item assessment, asks subjects' perception of the effects of the study medication on their sleep relative to their sleep before entering in the study

Other exploratory endpoints considered by the Applicant were not included in this efficacy review because they either did not contribute to the understanding of efficacy for the drug or were considered more suitable for the review of safety (e.g., fatigue severity scale and rebound insomnia).

Clinical Reviewer Comments: *The primary and secondary endpoints for Study 303 were based on self-reported sleep diary entries. Subjective sleep reports tend to correlate with objective polysomnography (PSG) data [26], however, it may have been challenging for some subjects to accurately recall and report multiple sleep parameters down to the minute every night for a year.*

The choice of change from baseline (CFB) to 6 months was longer than other insomnia drug development programs. This design choice is a strength for examining the effectiveness of longer-term treatment of insomnia disorder, which can be chronic. However, the 6-month endpoint could increase risk of drop out for non-responders and the placebo group, especially as subjects agreed not to seek other treatment for their insomnia. In total, the 6-month endpoint was considered appropriate given the Applicant's stated goal of pursuing lemborexant as a long-term treatment of insomnia disorder.

Sleep parameter definitions used by the Applicant in Study E2006-G000-303 are presented below in Table 27.

Table 27: Definition of Sleep Parameters for Study E2006-G000-303

Abbreviation	Sleep Parameter	Applicant Definition
sSE	Subjective Sleep Efficiency	Proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reports attempting to sleep until the time the subject stopped trying to sleep for the night (operationalized as the time the subject got out of bed for the day), and time spent asleep derived from subjective time spent in bed minus sWASO
sSOL	Subjective Sleep Onset Latency	Estimated minutes from the time that the subject attempted to sleep until sleep onset
sTST	Subjective Total Sleep Time	Derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
sWASO	Subjective Wake After Sleep Onset	Sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night, operationalized as the time the subject got out of bed for the day

Abbreviations: sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset
Source: Clinical Reviewer summary table using information from the Study 303 Core Clinical Study Report

8.1.1.2. Assessment Schedule:

The Applicant's schedule of events is detailed in Table 28.

Table 28: Applicant Schedule of Procedures/Assessments in Study E2006-G000-303

Phase	**Prerandomization**				**Randomization**																
	Screening		**Run -In[a]**	**Study Baseline**	**Treatment Period 1[a]**							**Treatment Period 2[a]**						**Follow-Up**		**ET/ EDD[b]**	**UNS [c]**
Visit[d]	1	2a	2b	3a	3b	4[d]	5[d]	6[d]	7[d,e]	8[d,e]	9[d]	10[d,e]	11[d,e]	12[d]	13[d,e]	14[d,e]	15[d]		EOS 16		
Day	-35 to -17	-17 to -14[f]	thru -1	1																	
Month[g]	–	–				1	2	3	4	5	6	7	8	9	10	11	12	(Wk 52 to 54)	(End Wk 54)		
Informed consent	X																				
Demographics	X																				
Inclusion/ exclusion criteria[h]	X	X		X																	
Sleep Disorders Screening Battery[i]	X																				
Sleep, medical, and psychiatric history	X																				
Physical examination[j]	X			X		X	X	X			X			X			X		X	X	X
Height	X																				
Vital signs	X			X		X	X	X			X			X			X		X	X	X
Weight	X			X		X	X	X			X			X			X		X	X	
Insomnia and Severity Index	X			X		X		X			X			X			X				
Fatigue Severity Scale	X			X		X		X			X			X			X				
Prior and concomitant medication(s)	← →																				

Phase	Prerandomization				Randomization																
	Screening		Run -In[a]	Study Baseline	Treatment Period 1[a]							Treatment Period 2[a]						Follow-Up		ET/ EDD[b]	UNS[c]
Beck Depression Inventory - II	X																				
Beck Anxiety Inventory	X																				
12-lead ECG[k]	X			X		X[l]		X[l]			X[l]			X[l]			X[l]		X[l]		
Urine pregnancy test[m]		X		X		X	X	X			X			X			X		X	X	
Serum pregnancy test (β-hCG)[m]	X																				
Urine drug test[n]	X	X		X		X	X	X			X			X			X		X	X[n]	X[n]
Serology (Hepatitis B and C)[o]	X																				
Clinical laboratory tests[p]	X			X		X		X			X			X			X		X	X	X
eC-SSRS	X			X		X		X			X			X			X		X	X	
Sleep diary[q]	◄																		►		
Dispense study drug			X		X	X	X	X			X			X							
Retrieve unused study drug				X		X	X	X			X			X			X				
Study drug compliance[r]				X		X	X	X			X			X			X				
Randomization					X[a,s]						X[a]										
EQ-5D-3L	X			X		X		X			X			X			X				
WPAI-GH	X			X				X			X			X			X				
PGI-Insomnia						X		X			X			X			X				
T-BWSQ																			X		
Adverse events[t]	◄																		►		

Phase	Prerandomization				Randomization															
	Screening		Run -In[a]	Study Baseline	Treatment Period 1[a]							Treatment Period 2[a]						Follow-Up		ET/ EDD[b]	UNS[c]
Lemborexant PK sampling (plasma)[u]						X		X			X			X			X			X[v]	X

Abbreviations: AE, adverse event; β-hCG, beta-human chorionic gonadotropin; ECG, electrocardiogram; eC-SSRS, electronic Columbia-Suicide Severity Rating Scale; EDD, early drug discontinuation; EOS, end of study; EQ-5D-3L, EuroQOL version 5D-3L; ET, early termination; HBsAG, hepatitis B surface antigen; HCV, human immunodeficiency virus; IgG, Immunoglobulin G; PGI-Insomnia; Patient Global Impression – Insomnia; PK, pharmacokinetics; T-BWSQ, Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; UNS, unscheduled; WPAI-GH, Work Productivity and Activity Impairment Questionnaire – General Health

[a] Subjects were not informed that placebo was to be administered during the Run-In Period. They were also not informed of the timing of the placebo-controlled period (Period 1) or the active-treatment (only) period (Period 2), and were not to be informed of the timing of the second randomization for subjects who received placebo during Period 1.

[b] These assessments were conducted at EOS, ET, and EDD (except the T-BWSQ, which will not be conducted at EDD). Subjects who discontinued study drug prematurely at any time after randomization at Visit 3 (Study Baseline) were encouraged to return to the site as soon as practicable (preferably within 7 days). These subjects were encouraged to continue to complete all study assessments (excepting PK samples, which will not be taken), including the Sleep Diary, and to return for all subsequent clinic visits, without the administration of study medication. Subjects who did not agree to this underwent an ET Visit and an EOS Visit. Subjects who did agree to continue with study procedures without the administration of study drug underwent an EDD Visit. These subjects needed not attend the next regularly scheduled visit if this failed within the visit window of the next visit. Subjects who discontinued early from study drug were considered on study as long as they returned for their regularly scheduled visits.

[c] Assessments during a UNS were to be performed at the discretion of the investigator.

[d] Visits 4, 5, and 6 were to be conducted within ±4 days of the schedule. Visits 7 through 15, and EOS were done within ±7 days of the schedule.

[e] The site telephoned the subject to assess AEs, to record concomitant medications, and to review the sleep diaries. If any AE was clinically significant and requires follow-up, a clinic visit should have been arranged (Unscheduled Visit).

[f] The Run-In Period could start between Day −17 and Day −14 and continued for approximately 14 consecutive days and a maximum of 17 days.

[g] Defined as a calendar month.

[h] Inclusion and exclusion criteria were to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2 of the protocol (Appendix 16.1.6).

[i] Sleep Disorders Screening Battery comprised: STOPBang, International Restless Legs Scale, and Epworth Sleepiness Scale.

[j] A full physical examination was carried out at Screening and EOS (ET at the discretion of the investigator) and included a brief neurological examination. A brief physical examination was carried out at other visits.

[k] The ECG should have been repeated if an abnormality was observed.

[l] If subject had a normal ECG baseline reading, but during any visit thereafter the QT is measured as >450 ms, 3 consecutive ECGs separated by 5 to 10 minutes were performed to confirm the abnormality.

[m] Female subjects of child-bearing only.

[n] Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at ET only for subjects who withdrew because of an AE.

[o] Viral screening for hepatitis B (HBsAG) and hepatitis C (HCV antibody IgG) were conducted.

[p] Clinical laboratory tests include hematology, blood chemistry, and urinalysis.

[q] Subjects should have completed the Sleep Diary, within 1 hour of waketime, each day throughout the study until EOS. Sleep diaries should have been reviewed for elig bility: for the 7 consecutive days immediately before Visit 2, and for the Run-In Period at Visit 3. Thereafter, the Sleep Diary should have been reviewed for completeness once a month.

[r] Study drug compliance (tablet count) was carried out at each clinic visit from Visit 3a through Visit 15.

[s] All other Baseline Period procedures were completed and subject eligibility confirmed before randomization took place and study drug was dispensed.

[t] At each visit, subjects were asked whether they had a fall since the previous visit. If yes, supplemental information was obtained to support a narrative for the event, per Section 9.2.5 Adjudication Committee in the protocol.

[u] PK: A single blood sample (approximately 4 mL) for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 were taken at each specified visit. The date and time of the 2 most recent doses administered before each sample was documented.

[v] PK sample was collected at ET visit (not at EOS).

Source: Applicant Clinical Study Report for E2006-G000-303, Taboke 4

8.1.1.3. Statistical Analysis Plan

The statistical plan was finalized before the data were unblinded. At the pre-NDA meeting held on June 14, 2018, the Agency raised concerns about the proposed primary analysis method which was based on missing data imputation using a complete case missing value (CCMC) assumption. The Agency also raised concerns on the interpretability of Eisai's proposed tipping point analysis (TPA). The Applicant agreed to amended statistical analysis plan with the details of the revised TPA.

The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The change from baseline of log(sSOL), SE and sWASO, which were measured at the first 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5 and Month 6, were analyzed using the mixed effect model repeated measurement (MMRM) analysis on the FAS. The model was adjusted for the corresponding Study Baseline value, region (North America, Europe and New Zealand, Asia), age group (<65 years old, ≥65 years old), treatment, time (first 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5 and Month 6) and the interaction of treatment by time. Since the Applicant considered sSOL to be non-normally distributed and the Agency had no evidence to against the assumption, a log-transformation was used in the primary analysis. The distribution of the sSOL was explored. The unstructured covariance matrix (UN) was used in the analysis. In the case of nonconvergence of UN, the Toeplitz covariance matrix (TOEP) would be used. In the case of nonconvergence with TOEP, the autoregressive covariance matrix [AR (1)] would be used in the model.

Before the implementation of the MMRM model, the missing values were imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed all primary efficacy assessments without missing values). The missing values for a given visit were imputed using all available values including the retrieved measurement from the post-discontinuation data. The treatment comparisons were performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment differences were also provided.

A sequential gate-keeping procedure was used for primary endpoint and secondary endpoint comparisons to control for the overall type 1 error at the 0.05 significance level. The first endpoint comparison was tested at the 0.05 significance level. If the primary endpoint was found to be statistically significant, then the testing of the next endpoint processed at the significance level of 0.05; testing would not proceed if the result on a test was insignificant.

The primary endpoints were tested in the following order:

1. Change from Study Baseline at Month 6 in log(sSOL), LEM10 compared to PBO
2. Change from Study Baseline at Month 6 in log(sSOL), LEM5 compared to PBO

The key secondary endpoints were only tested if both primary analyses were statistically significant at the 0.05 level. The key secondary endpoints were tested in the following order:

1. Change from Study Baseline at Month 6 in sSE, LEM10 compared to PBO
2. Change from Study Baseline at Month 6 in sSE, LEM5 compared to PBO
3. Change from Study Baseline at Month 6 in sWASO, LEM10 compared to PBO
4. Change from Study Baseline at Month 6 in sWASO, LEM5 compared to PBO

The following sensitivity analyses were performed on the primary endpoint and the key secondary endpoints: MMRM analysis with MI imputation assuming CCMV-7, tipping point analysis, and MMRM assuming MAR.

Protocol Amendments

Version 1 of the protocol was dated April 16, 2016. The Protocol was amended six times and revised seven times. See Table 29 below for a review of relevant revisions to the protocol. The amendments seemed reasonably appropriate.

Table 29: Revisions and Amendments to the E2006-G000-303 Protocol

Date	Key Items
7/15/2016	• Revised STOPBang score cutoff for exclusion from study. • Revised Epworth Sleepiness Scale score cutoff for exclusion from study. • Stated that subjects taking sedating drugs that would interfere with occupation or activities were excluded. • Revised the washout interval between taking a prohibited medication, including treatment for insomnia, and the first dose of study drug. • Allowed flexibility for the means of documenting the time and date of 2 most recent doses before each blood sample for pharmacokinetic analyses. pharmacokinetic analyses. • Revised method for assessment of rebound insomnia. • Provided that for applicable countries, the year of birth were collected instead of the date of birth. • Specified viral tests for hepatitis B and hepatitis C. • Deleted alcohol and nicotine/cotinine from screening for drugs of abuse. • Deleted glucose-metabolizing agents
9/29/2016	• Stated that enrollment of subjects <65 years would be limited if the percentage of enrolled subjects >65 years was below expectations toward the end of the study. • Clarified that subjects who discontinued study medication but did not agree to return for study visits underwent an EOS visit. • Clarified the term abstinence. • Clarified excessive caffeine use. • Clarified that subjects who lacked capacity and/or whose cognitive decline indicated disorientation to person/place/time and/or situation are excluded. • Specified that the statistical model included region if necessary, that countries with small numbers of subjects would be pooled by region, and that regions were grouped in consideration of the number and homogeneity of subjects from each region. • Specified that informed consent was taken by personnel in accordance with national legislation. • Clarified the reason why subjects should not eat a meal within 3 hours before taking the study drug. • Specified that the neurological examination was conducted by a clinician whose clinical experience ensured that an adequate assessment of domains underlying the exclusion criteria could be performed. • Specified that the investigator agreed to allow direct access to source documents and study facilities to sponsor representative(s),monitor(s) and auditor(s), and agree to inspection by regulatory

Date	Key Items
	authorities or IRB/IEC representative.
10/25/2016	Revised exclusion criteria regarding highly effective forms of contraception.
5/6/2017	• Revised approximate number of sites from 110 to 125. • Revised to Screening Period from up to –28 days to up to –35 days. • Revised the requirement for a history of "difficulties with sleep onset and sleep maintenance" to "difficulties with sleep onset and/or sleep maintenance". • Deleted "or early morning awakening" from the requirements. • Deleted the MUPS and revised text such that investigators instead interview subjects regarding possible history of parasomnias. • Revised inclusion (#3, 7, and 10) from sSOL ≥30 AND sWASO ≥60 minutes to sSOL ≥30 minutes AND/OR sWASO ≥60 minutes. • Revised inclusion (#5) for regular bedtime from between 21:00 and 24:00 to between 21:00 and 01:00, waketime from between 05:00 and 09:00 to between 05:00 and 10:00. • Revised inclusion (#8) requiring the subjects had a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours. • Revised inclusion (#9) requiring maximum duration of time spent in bed from 9 hours to 10 hours, on Sleep Diary at Visit 2a. • Revised inclusion (#11) requiring reconfirmation of regular bedtimes and waketimes during Run-in Period. • Revised inclusion (#12) to delete requirement for no more than 2 nights with duration of time in bed >9 hours in Run-in. • Revised exclusion (#1) from ESS score ">10" to ">15" as an indicator of excessive daytime sleepiness and required that scores of 11 to 15 be recorded as excessive daytime sleepiness in subject's Medical History). • Revised exclusion (#3) to remove MUPS assessment and allow evaluation based upon reporting of a history of sleep-related violent behavior or sleep driving, or any other complex sleep related behavior (e.g., making phone call or preparing and eating food while sleeping). • Revised exclusion (#20) for suicidal behavior as per the C-SSRS from "lifetime" to "in the past 10 years". • Revised exclusion (#21) to specify major surgery. • Revised name and description of Adjudication Committee and added seizures as adverse events to be adjudicated. • Added requirement to question subjects as to whether they had a fall, at each visit, and record supplemental information. • Revised analyses for Primary, Secondary and Exploratory Efficacy. • Revised definitions of prior and concomitant medications. • Revised List of Prohibited Concomitant Medications. • Added the requirement of a Data Safety Monitoring Board. • Converted Month 2 visit from phone to in-person visit.
6/28/2018	• Added analysis of Treatment Period 1. Based on the results of pivotal Study 304 and special safety studies, the Applicant decided to include a database lock with interim analysis to assess efficacy in the double-blind placebo-controlled treatment period. All available safety data were assessed. • In the event of an interim analysis, Applicant staff would be unblinded; however, site personnel, investigator, and subjects would remain blinded • To align with Regulatory Authority provision
8/3/2018	• Updated interim analysis description (to clarify that no interim analysis was being performed and that when all subjects had completed Period 1, all data were unblinded to the Applicant and that study sites and subjects would remain blinded until the study had been completed.)

Date	Key Items
8/13/2018	• Updated list of prohibited concomitant medications to prohibit moderate CYP3A inhibitors • Revised other secondary endpoint analyses for FSS

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; CYP, cytochrome P450; EOS, end of study; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; IEC, Independent Ethics Committee; IRB, Institutional Review Board; sSOL, subjective sleep onset latency; MUPS, Munich Parasomnia Scale; sWASO, subjective wake after sleep onset
a: The number of subjects in the study under each amendment
Source: Modified from Applicant's Table 8, "Revisions to the Protocol, Including Protocol Amendments" Applicant's Clinical Study Report for E2006-G000-303

Other relevant agreed-upon items are listed below:

May 2015: Agreement on proposed revisions to the phase 3 program (extending the treatment period of Study E2006-G000-303 from 6 months to 12 months and thereby eliminating Study E2006-G000-307)

January 2018:

- Acceptability of 40% elderly enrolled in phase 3 program (per End of Phase 2 Meeting) would ultimately be a review issue
- Agreement with the sleep-onset primary endpoint of PSG-determined latency to persistent sleep (LPS; study -304); substantiated by subjective Sleep Onset Latency (sSOL; study -303)
- Recommendation to use PSG-measured Wake After Sleep Onset (WASO) versus placebo as a key secondary endpoint, with subjective WASO used for substantiation in the second study

8.1.1.4. Study Results for E2006-G000-303

The Applicant provided several analysis sets for Study 303. The number of patients per treatment arm in the analysis datasets are presented in Table 31.

Table 30: Applicant's Description of Analysis Sets Used in E2006-G000-303

		Lemborexant		Combined
	Placebo (N=325) n (%)	5 mg (N=323) n (%)	10 mg (N=323) n (%)	Total (N=971) n (%)
Safety Analysis Set[a]	319 (98.2)	314 (97.2)	314 (97.2)	947 (97.5)
Full Analysis Set[b]	318 (97.8)	316 (97.8)	315 (97.5)	949 (97.7)
Per Protocol Analysis Set[c]	306 (94.2)	309 (95.7)	306 (94.7)	921 (94.9)
6-Months Completer Analysis Set[d]	217 (66.8)	213 (65.9)	209 (64.7)	639 (65.8)

Abbreviations: FAS, Full Analysis Set; SAP, statistical analysis plan.
a: Safety Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
b: Full Analysis Set is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement.
c: Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria are specified in the SAP.
d: The 6-Months Completer Analysis Set is the group of subjects in the FAS who had all efficacy assessments up to and including Month 6 (i.e., Week 1 and Months 1 to 6 visits) without missing primary or key secondary efficacy assessments at any of these visits.
Source: Applicant's Clinical Study Report for E2006-G000-303

Compliance with Good Clinical Practices

According to the Applicant, this study was performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities.

Financial Disclosure
The Applicant submitted the expected financial certification and disclosure statement, per 21 CFR 314.50(k), for all clinical investigators who participated in Study E2006-G000-303, as agreed with the Division at the Type B pre-NDA meeting. There were no notable disclosures. See Section 14.2, *Financial Disclosures.*

Patient Disposition
This study started on November 15, 2016 (date of first subject enrolled), and the date of the last subject's completion of Period 1 was May 31, 2018. A total of 2059 subjects signed informed consent for entry into the study. Of these, 1088 (52.8%) subjects were screening failures, 1341 (65.1%) subjects continued into the Run-in Period, and 971 (47.1%) continued into the Treatment Period. The main reasons for screening failure were subjects not meeting inclusion/exclusion criteria (937 [45.5%] subjects) followed by withdrawal of consent (88 [4.3%] subjects).

A total of 971 subjects were randomized in phase 1 (323 in LEM10, 323 in LEM5, 325 in PBO). Twelve of the randomized subjects were not treated with study drug (4 subjects in each of the LEM10, LEM5, and PBO treatment groups). Of the 959 treated subjects, 10 subjects (4 in LEM10, 3 in LEM5 and 3 in PBO) did not have postdose primary efficacy measurements. Therefore, 949 subjects (315 in LEM10, 316 in LEM5, 318 in PBO) were included in the FAS. The majority (70.8% in LEM10, 78.7% in LEM5 and 80.1% in PBO) of randomized subjects completed the treatment through Month 6.

Period 1 of Study 303 had a total drop out/discontinuation rate of 20.5% (N=131) at 6 months. The dropout rate for the placebo arm was 18.1% (N=58). The most frequent reasons for discontinuation from the placebo group were inadequate therapeutic effect (5.3%), subject choice (4.7%), and withdrawal of consent (4.0%). The dropout rate for LEM10 was 25.1% and LEM5 was 18.1%. The most frequently reported reasons for drop out for included subject choice (5.3% for LEM10 and 3.4% for LEM5); adverse events (4.7% in LEM10 vs 2.2% in LEM5). Table 31 below lists the subject-reported reasons for discontinuation.

Table 31: Subject Disposition and Reason for Discontinuation From Study 303 Period 1

		Lemborexant		
	Placebo	**5 mg**	**10 mg**	**Total**
Randomized, n	325	323	323	646
Not treated, n	4	4	4	8
Treated, n (%)	321 (100)	319 (100)	319 (100)	638 (100)
Completed the Study Period 1, n (%)	257 (80.1)	251 (78.7)	226 (70.8)	477 (74.8)
Discontinued from the Study Period 1, n (%)	58 (18.1)	51 (16.0)	80 (25.1)	131 (20.5)
Primary reason(s) for discontinuation[a], n (%)	58 (18.1)	51 (16.0)	80 (25.1)	131 (20.5)
Adverse event[b]	8 (2.5)	7 (2.2)	15 (4.7)	22 (3.4)
Lost to follow-up	5 (1.6)	3 (0.9)	6 (1.9)	9 (1.4)
Subject choice	15 (4.7)	11 (3.4)	17 (5.3)	28 (4.4)
Inadequate therapeutic effect	17 (5.3)	9 (2.8)	11 (3.4)	20 (3.1)
Withdrawal of consent	13 (4.0)	10 (3.1)	20 (6.3)	30 (4.7)
Other	0	11 (3.4)	11 (3.4)	22 (3.4)
Other reason(s) for discontinuation[a], n (%)	10 (3.1)	6 (1.9)	14 (4.4)	20 (3.1)
Adverse event[b]	0	0	0	0
Subject choice	6 (1.9)	2 (0.6)	6 (1.9)	8 (1.3)
Inadequate therapeutic effect	3 (0.9)	3 (0.9)	5 (1.6)	8 (1.3)
Other	2 (0.6)	1 (0.3)	4 (1.3)	5 (0.8)
Discontinued from study treatment but continued in the study, n (%)	3 (0.9)	6 (1.9)	12 (3.8)	18 (2.8)

For a total of 23 subjects. the completion/discontinuation box on the Disposition (Study Phase) page of the CRF was not checked.
Percentages are based on the number of subjects randomized and treated in the relevant treatment group. The treatment group is based on the assignment of subjects in the Period 1.
AE, adverse event; CRF, case report form
a: As reported on the Subject Disposition CRF.
b: Corresponding AEs leading to withdrawal from the study or study drug were reported on the AE CRF. Source: Table 14.1.1.3.2
Source: Applicant's Clinical Study Report for E2006-G000-303, Table 9

Clinical Reviewer Comments: *The discontinuation rate for LEM5 (16.0%) was similar to placebo (18.1%) and lower than that higher for LEM10 (25.1%). The dropout rate for adverse events was more than double for participants in the LEM10 group compared to LEM5 or placebo. For those that discontinued LEM10, the top two reasons (<5%) listed were withdrawal of consent and subject choice. Adverse event was listed as the discontinuation reason for 4.7% of LEM10 subjects and 2.2% of LEM5 subjects.*

8.1.1.5. Protocol Violations/Deviations

Protocol deviations were identified, reviewed, and documented by the Applicant's clinical team prior to database lock/treatment unblinding. All protocol deviations were categorized as major/minor and by standard classifications including but not limited to the following:

- Violations of inclusion/exclusion criteria
- Noncompliance with or incorrect implementation of protocol procedures
- Noncompliance of randomized study drug and dosage
- Use of prohibited concomitant medication

Major protocol deviations are summarized by category and treatment group in Table 32. The Applicant reported that 27 (2.8%) of subjects had one or more major protocol deviations, with a generally similar percentage per treatment arm. The three most common deviations were prohibited concomitant medication, study procedures/assessments, and visit scheduling.

Table 32: Applicant Summary of Major Protocol Deviations Study 303, Full Analysis Set

Summary of Major Protocol Deviations
Full Analysis Set

		Lemborexant			
	Placebo (N=318) n (%)	5 mg (N=316) n (%)	10 mg (N=315) n (%)	Total (N=631) n (%)	Combined Total (N=949) n (%)
Subjects with any major protocol deviations	13 (4.1)	6 (1.9)	8 (2.5)	14 (2.2)	27 (2.8)
Concomitant Medication	3 (0.9)	0	4 (1.3)	4 (0.6)	7 (0.7)
Other Protocol Deviation	1 (0.3)	1 (0.3)	0	1 (0.2)	2 (0.2)
Study Procedures/Assessments	4 (1.3)	2 (0.6)	1 (0.3)	3 (0.5)	7 (0.7)
Study Treatment Admin/Dispense	3 (0.9)	0	0	0	3 (0.3)
Study Treatment Compliance	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.3)
Visit Scheduling	1 (0.3)	2 (0.6)	2 (0.6)	4 (0.6)	5 (0.5)

Source: Applicant's Clinical Study Report for E2006-G000-303, Table 14.1.2

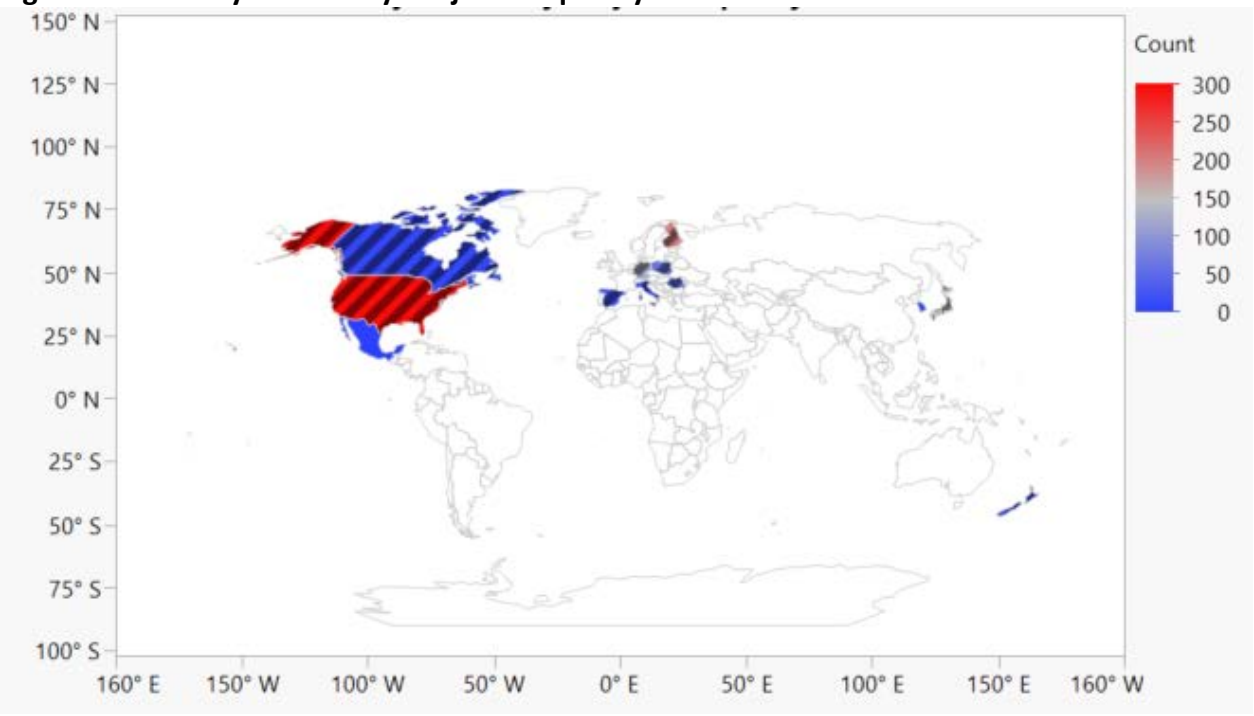
The Applicant's protocol deviations database for Study E2006-G000-303 listed the very brief details for seven protocol deviations due to concomitant medications (Source, Study 303 CSR, Listing 16.2.2.1). Subject (b) (6) (LEM5) was administered doxylamine and Subject (b) (6) (Placebo in Period 1, LEM5 in Period 2) was administered Imovane (Zopiclone); both are prohibited concomitant medications that could cause sedation and influence outcomes, depending on the timing of the protocol deviation. Three subjects had no drug listed in the provided log, so the effect is unknown. The seventh subject was administered a prohibited concomitant medication (methylprednisolone), which is not likely influence efficacy results unless taken chronically, but the details of how the medication was taken were not provided for any of the aforementioned concomitant medication protocol deviations.

Clinical Reviewer Comments*: The frequencies of major protocol deviations are considered to be relatively low (ranging from 1.9% to 4.1% across the treatment arms) and do not raise broader concerns about data integrity. The deviations are reasonably balanced across treatment arms and are not expected to confound interpretation of efficacy findings.*

8.1.1.6. Demographic Characteristics for E2006-G000-303

The trial for E2006-G000-303 (hereafter referred to as Study 303) included 119 enrollment sites, of which 101 sites have at least one randomized patient (41 sites in North America, 43 sites in Europe and New Zealand, and 26 sites in Asia).

Figure 17: Country Colored by Subject Frequency



Source: Clinical reviewer generated figure from Study E2006-G000-303 adsl dataset

Table 33 lists the baseline demographic characteristics for Study 303. The majority of subjects were female (68.2%) and white (71.5%); the median age was 55.0 years (range: 18 to 88 years). In general, baseline demographic characteristics were similar across treatment groups. Other than the higher percentage of females, the baseline characteristics appear consistent with the general population of adults who may seek treatment for insomnia disorder.

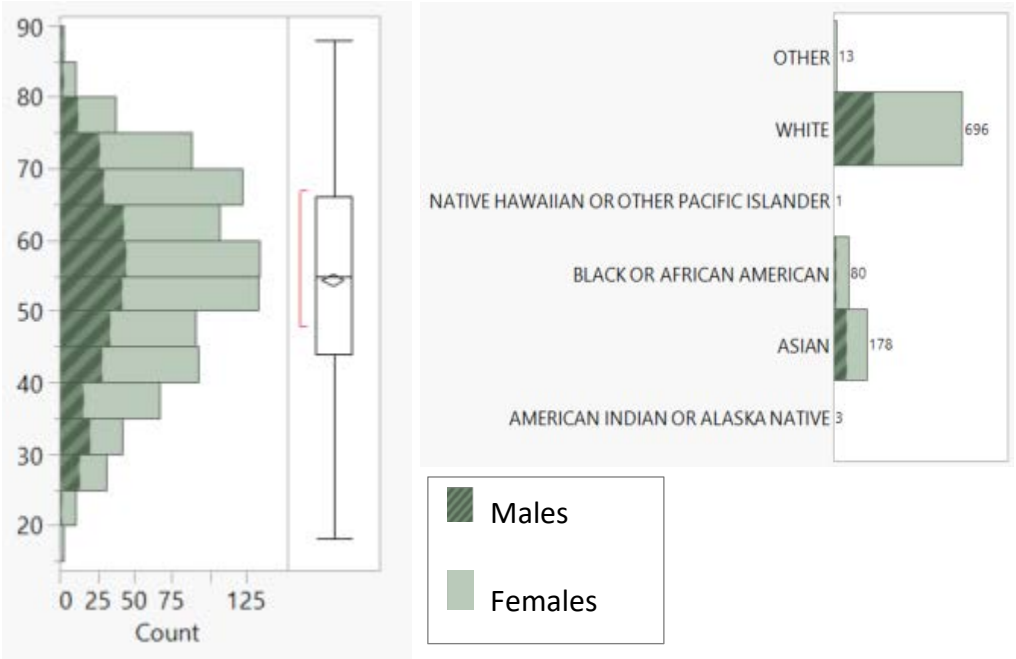
Table 33: Demographic Characteristics of the Full Analysis Set for E2006-G000-303

Demographic Parameters	Placebo (N=318)	Lemborexant 5 mg (N=316)	Lemborexant 10 mg (N=315)	Total (N=949)
Sex				
Male	102 (32.1)	107 (33.9)	93 (29.5)	302 (31.8)
Female	216 (67.9)	209 (66.1)	222 (70.5)	647 (68.2)
Age				
Mean years (SD)	54.5 (14.01)	54.2 (13.74)	54.8 (13.68)	54.5 (13.80)
Median (years)	56.0	55.0	55.0	55.0
Min, max (years)	18, 83	20, 85	18, 88	18, 88
Age Group				
< 65 years	229 (72.0)	229 (72.5)	229 (72.7)	687 (72.4)
≥ 65 years	89 (28.0)	87 (27.5)	86 (27.3)	262 (27.6)
Race				
White	232 (73.0)	222 (70.3)	225 (71.4)	679 (71.5)
Black or African American	23 (7.2)	27 (8.5)	26 (8.3)	76 (8.0)
Asian	59 (18.6)	61 (19.3)	58 (18.4)	178 (18.8)
Other[1]	4 (1.3)	6 (1.9)	6 (1.9)	16 (1.7)
Ethnicity				
Hispanic or Latino	34 (10.7)	19 (6.0)	19 (6.0)	72 (7.6)
Not Hispanic or Latino	284 (89.3)	297 (94.0)	296 (94.0)	877 (92.4)
Region				
North America	99 (31.1)	102 (32.3)	101 (32.1)	302 (31.8)
Europe and New Zealand	164 (51.6)	159 (50.3)	160 (50.8)	483 (50.9)
Asia	55 (17.3)	55 (17.4)	54 (17.1)	164 (17.3)

Abbreviation: SD, standard deviation
Source: Biostatistics Reviewer's Analysis (adsl.xpt)

Figure 18 reflects the distribution of age (mean age 54.32, SD 13.74) and race (White 71.68; Asian 18.33%; Black 8.23%; American Indian or Alaska Native 0.31%; Other 1.33%) for subjects randomized to treatment in Study 303. Note the disproportionally higher percentage of females in across each age range and race.

Figure 18: Distribution of Age, Race, and Sex



Source: Clinical Reviewer figure generated from E2006-G000-303 adsl dataset

Other Baseline Characteristics

Table 34 below highlights baseline characteristics from all randomized subjects for Study 303.

Table 34: Other Baseline Characteristics (Height, Weight, BMI), Full Analysis Set for E2006-G000-303

		Lemborexant			
	Placebo (N=318)	5 mg (N=316)	10 mg (N=315)	Total (N=631)	Combined Total (N=949)
Weight (kg)					
n	318	316	315	631	949
Mean (SD)	75.79 (17.143)	75.94 (18.182)	75.94 (17.803)	75.94 (17.979)	75.89 (17.695)
Median	74.00	73.75	73.90	73.80	73.90
Min, Max	41.3, 155.0	37.0, 164.0	40.0, 168.0	37.0, 168.0	37.0, 168.0
Height (cm)					
n	318	316	315	631	949
Mean (SD)	166.64 (9.808)	166.73 (9.593)	166.69 (8.860)	166.71 (9.227)	166.69 (9.421)
Median	165.05	165.00	166.00	166.00	165.50
Min, Max	145.0, 197.0	141.0, 196.6	145.0, 191.0	141.0, 196.6	141.0, 197.0
BMI (kg/m²)					
n	318	316	315	631	949
Mean (SD)	27.23 (5.540)	27.30 (6.266)	27.23 (5.625)	27.26 (5.950)	27.25 (5.813)
Median	26.21	26.45	26.73	26.53	26.44
Min, Max	17.0, 54.9	14.4, 62.1	15.8, 60.2	14.4, 62.1	14.4, 62.1
BMI group (kg/m²), n (%)					
< 18.5	7 (2.2)	6 (1.9)	5 (1.6)	11 (1.7)	18 (1.9)
18.5 to < 25	115 (36.2)	124 (39.2)	107 (34.0)	231 (36.6)	346 (36.5)
25 to 30	112 (35.2)	114 (36.1)	123 (39.0)	237 (37.6)	349 (36.8)
> 30	84 (26.4)	72 (22.8)	80 (25.4)	152 (24.1)	236 (24.9)

Source: Listing 16.2.4.1
Percentages are based on the total number of subjects with non-missing values in the relevant treatment group.
BMI = Body Mass Index.
a: Age is calculated at Date of Informed Consent.
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Source: Applicant's Clinical Study Report for E2006-G000-303, Table 14.1.4.1.1.2

The Applicant provided baseline scores on primary and key secondary efficacy measures according to treatment group (Table 35). The differences between baseline subjective sleep parameters among placebo, LEM5 and LEM10 does not appear clinically significant. Baseline scores from the full analysis set for ISI, FSS, BDI-II and BAI were also similar across groups.

Table 35: Baseline Scores for Primary and Key Secondary Endpoints in E2006-G000-303

		Lemborexant			
Category	Placebo (N=318)	5 mg (N=316)	10 mg (N=315)	Total (N=631)	Combined Total (N=949)
sSOL (minutes)					
n	316	314	312	626	942
Mean (SD)	64.03 (45.209)	62.19 (45.674)	64.97 (44.020)	63.58 (44.843)	63.73 (44.943)
Median	55.86	53.57	55.71	54.64	55.21
Min, Max	5.1, 411.4	3.6, 445.7	6.3, 360.0	3.6, 445.7	3.6, 445.7
sSE (%)					
n	307	302	299	601	908
Mean (SD)	61.34 (17.836)	63.14 (18.231)	62.03 (17.248)	62.59 (17.742)	62.17 (17.774)
Median	63.47	67.00	65.05	65.98	65.42
Min, Max	14.6, 92.1	0.0, 93.5	9.2, 94.2	0.0, 94.2	0.0, 94.2
sWASO (minutes)					
n	314	313	311	624	938
Mean (SD)	132.49 (80.198)	132.77 (82.518)	136.83 (87.391)	134.79 (84.938)	134.02 (83.345)
Median	120.00	114.71	120.57	115.71	117.71
Min, Max	1.4, 420.0	0.0, 430.0	0.7, 460.0	0.0, 460.0	0.0, 460.0
sTST (minutes)					
n	307	302	299	601	908
Mean (SD)	304.25 (91.459)	315.52 (93.498)	306.89 (88.031)	311.23 (90.846)	308.87 (91.063)
Median	314.71	332.14	315.33	324.29	320.64
Min, Max	70.0, 487.9	0.0, 531.2	38.6, 495.6	0.0, 531.2	0.0, 531.2

Abbreviations: SD, standard deviation; sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO: subjective wake after sleep onset
Source: Applicant's Clinical Study Report for E2006-G000-303, Table 14.1.4.1.2.2.1

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Compliance: The Applicant calculated compliance as follows:

$$\frac{100 \times (\text{Total number of tablets dispensed} - \text{Total number of tablets returned or lost})}{\text{Number of tablets expected to be taken}}$$

Table 36 details compliance by treatment arm. The majority of subjects (99.0%) were ≥80% to ≤100% compliant with study drug during the Run-in Period for the Safety Analysis Set, as assessed by pill counts. During Period 1, the majority of subjects (>92% across the treatment arms) were ≥80% to ≤100% compliant with study medication (see Table 36). Overall, during Period 1, three subjects (2 subjects for LEM10 and 1 subject for PBO) were >120% compliant with study medication. The percentage is based on the above calculation. Therefore, the result could be related to error, miscalculation, or requiring additional medication due to running out early due to product loss or taking more than the indicated dose.

Table 36: Study Medication Compliance During Study E2006-G000-303 Period 1, Safety Analysis Set

Category Parameter	Placebo (N=319)	Lemborexant 5 mg (N=314)	Lemborexant 10 mg (N=314)	Lemborexant Total (N=628)
Compliance categories, n (%)				
<80%	7 (2.2)	4 (1.3)	4 (1.3)	8 (1.3)
>=80 to <=100%	294 (92.2)	295 (93.9)	294 (93.6)	589 (93.8)
>100 to <=120%	17 (5.3)	15 (4.8)	13 (4.1)	28 (4.5)
>120%	1 (0.3)	0	2 (0.6)	2 (0.3)
Missing	0	0	1	1
Compliance rate				
n	319	314	313	627
Mean (SD)	98.6 (7.98)	98.2 (5.72)	99.3 (15.84)	98.8 (11.91)
Median	100.0	100.0	100.0	100.0
Min, Max	52, 210	41, 113	50, 356	41, 356

Abbreviation: SD, standard deviation
Source: Applicant's Clinical Study Report for E2006-G000-303, Table 14.1.5.1.2

Concomitant Medications: The baseline use of concomitant medications was similar across groups, ranging from 69.4 to 74.8%. During the treatment period, the range was 77.1 to 82.8%. The most commonly reported concomitant medications during Period 1 in the LEM10, LEM5, and PBO treatment groups were ibuprofen (15.9%, 21.7%, and 15.7% of subjects, respectively) and acetaminophen/paracetamol (12.1%, 11.1%, and 14.1% of subjects, respectively).

Clinical Reviewer Comments*: Concomitant medication use can potentially confound study results, and the study was not designed to determine their influence on efficacy (e.g., the timing, dosages, durations, and reasons for the concomitant medication use were not described). For example, the use of ibuprofen and paracetamol could be used to treat pain to aid in falling asleep at night or be used to treat a fever. However, the rates of concomitant medication use were reasonably balanced across groups and are not expected to impact the interpretation of study results.*

Rescue Medications: Rescue medications were not permitted during the study. Aberrant use of rescue medications is described in Section 8.1.1.5. *Protocol Violations/Deviations*.

8.1.1.7. Efficacy Results – Primary Endpoint

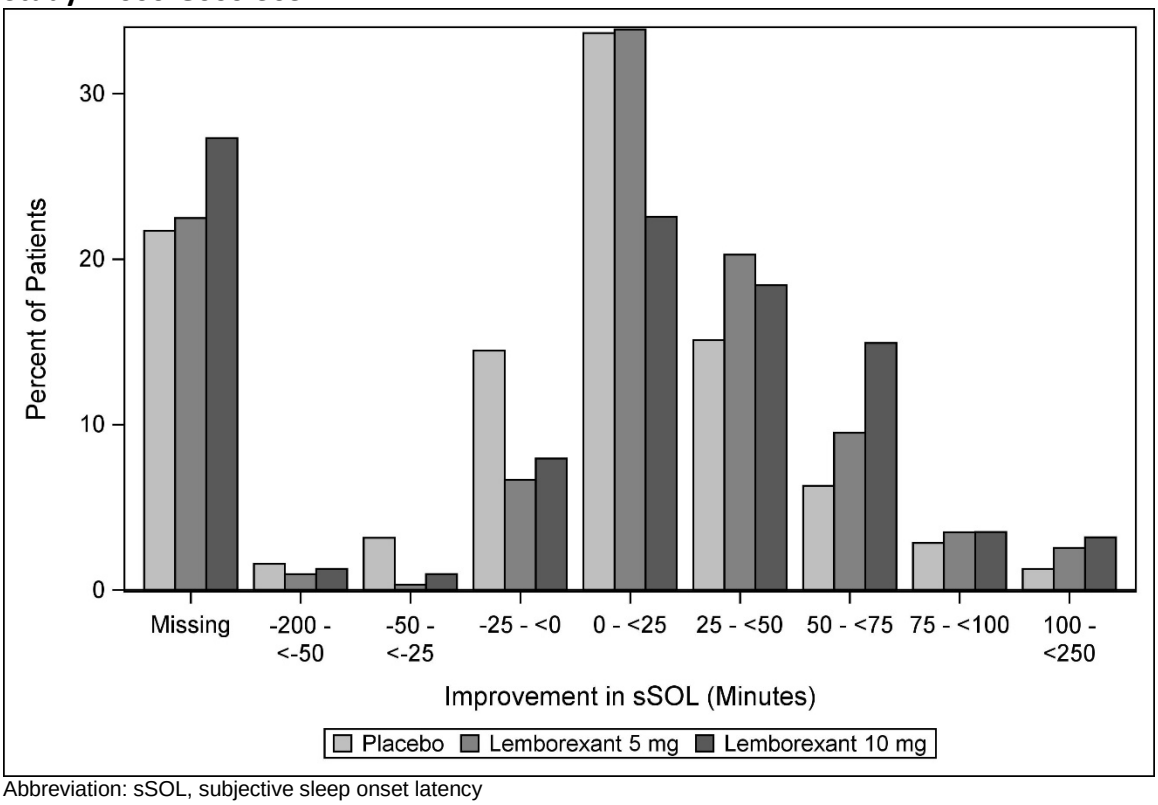
The primary analysis results for the primary efficacy endpoint according to the hierarchical testing procedure are provided in Table 37. The results on the primary efficacy endpoint were considered statistically significant for lemborexant 5 mg and 10 mg. Figure 19 displays histograms of the magnitude of improvement from baseline in sSOL at Month 6. To explore the distribution of sSOL, histograms of baseline sSOL and log(sSOL) with normal density are presented in Figure 20 and Figure 21. Based on the plots, the assumption of log normal distribution of sSOL seems reasonable. Before the NDA submission, FDA had concerns about the missing data imputation for the primary analysis. The missing values were imputed using a pattern mixture model utilizing multiple imputation assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed all primary efficacy assessments without missing values). To assess the robustness of the primary analysis results, the FDA statistical reviewer performed two sensitivity analyses: MMRM analysis without missing data imputation and pattern mixture imputation based on jump to placebo. MMRM analysis without missing data imputation assumes that the missing data mechanism is missing at random (MAR). The results from the MMRM analysis without imputation (Table 38) are very similar to the primary analysis results. The other sensitivity analysis that the FDA reviewer performed is pattern mixture imputation based on jump to placebo. This method assumes that the missing data mechanism is missing not at random (MNAR). An imputation model for the missing observations in the treatment group is constructed not from the observed data in the treatment group but rather from the observed data in the placebo group. The results (Table 39) are still very similar to the primary analysis results. The Applicant also performed several sensitivity analyses. The MMRM analysis with multiple imputation assuming CCMV-7 yields very similar results.

Table 37: Primary Efficacy Results on sSOL (Minutes), Study E2006-G000-303

Treatment Group	# ITT subjects	Baseline Geomean Score (SD)	Month 6 LSGM (SE)	LSGM ratio: Month 6 /Baseline (95% CI)	LSGM Treatment Ratio: Active /Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	318	45.0 (31.8)	27.3 (1.4)	0.62 (0.56, 0.68)		
Lemborexant 5 mg	316	43.0 (31.5)	20.0 (1.1)	0.45 (0.41, 0.50)	0.73 (0.64, 0.84) <0.001	Yes
Lemborexant 10 mg	315	45.0 (33.4)	19.2 (1.1)	0.43 (0.39, 0.48)	0.70 (0.61, 0.81) <0.001	Yes

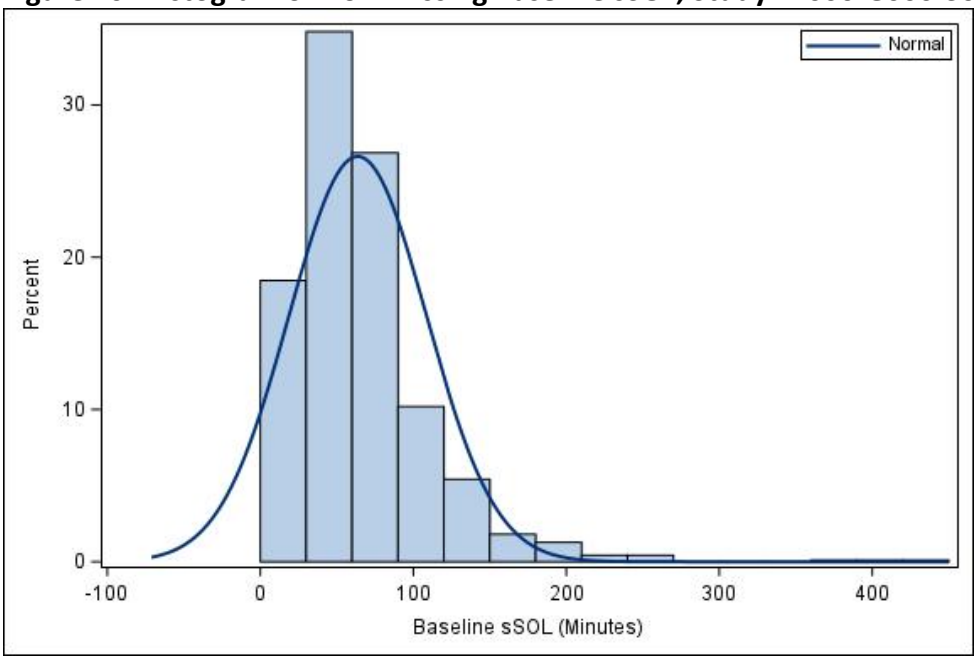
Abbreviations: CI, confidence interval; ITT, intention to treat; LSGM, least squares geometric mean; MCP, multiple comparison procedures; SD, standard deviation; SE, standard error; sSOL, subjective sleep onset latency
Note: CI were not adjusted with multiplicity
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 19: Histogram of the Magnitude of Improvement from Baseline in sSOL at Month 6, Study E2006-G000-303



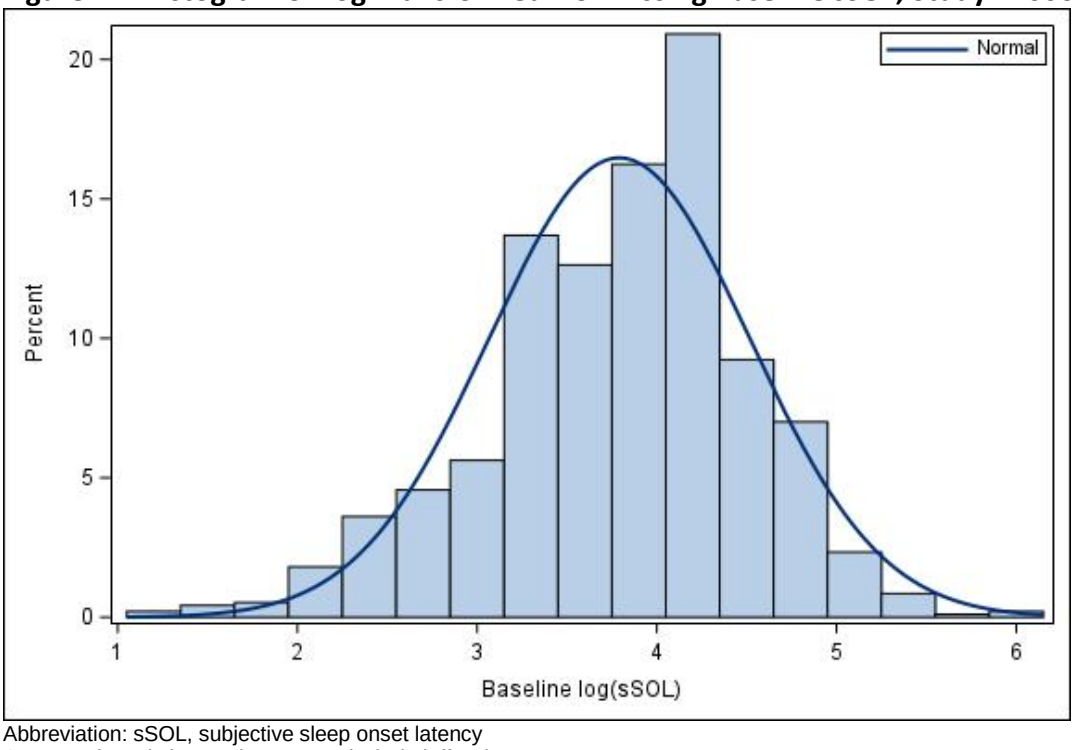
Abbreviation: sSOL, subjective sleep onset latency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 20: Histogram of Non-Missing Baseline sSOL, Study E2006-G000-303



Abbreviation: sSOL, subjective sleep onset latency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 21: Histogram of Log Transformed Nonmissing Baseline sSOL, Study E2006-G000-303



Abbreviation: sSOL, subjective sleep onset latency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Table 38: Sensitivity Analysis: MMRM Without Imputation Analysis Results on sSOL (Minutes), Study E2006-G000-303

Treatment Group	# ITT subject	Baseline Geomean Score (SD)	LSGM ratio: Month 6 /Baseline (95% CI)	LSGM Treatment Ratio: Active /Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	318	45.0 (31.8)	0.62 (0.56, 0.69)		
Lemborexant 5 mg	316	43.0 (31.5)	0.45 (0.41, 0.51)	0.73 (0.63, 0.85) <0.001	Yes
Lemborexant 10 mg	315	45.0 (33.4)	0.44 (0.39, 0.49)	0.70 (0.61, 0.82) <0.001	Yes

Abbreviations: CI, confidence interval; ITT, intention to treat; LSGM, least squares geometric mean; MCP, multiple comparison procedures; MMRM, mixed effect model repeated measurement; SD, standard deviation; sSOL, subjective sleep onset latency
Note: CI were not adjusted with multiplicity
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

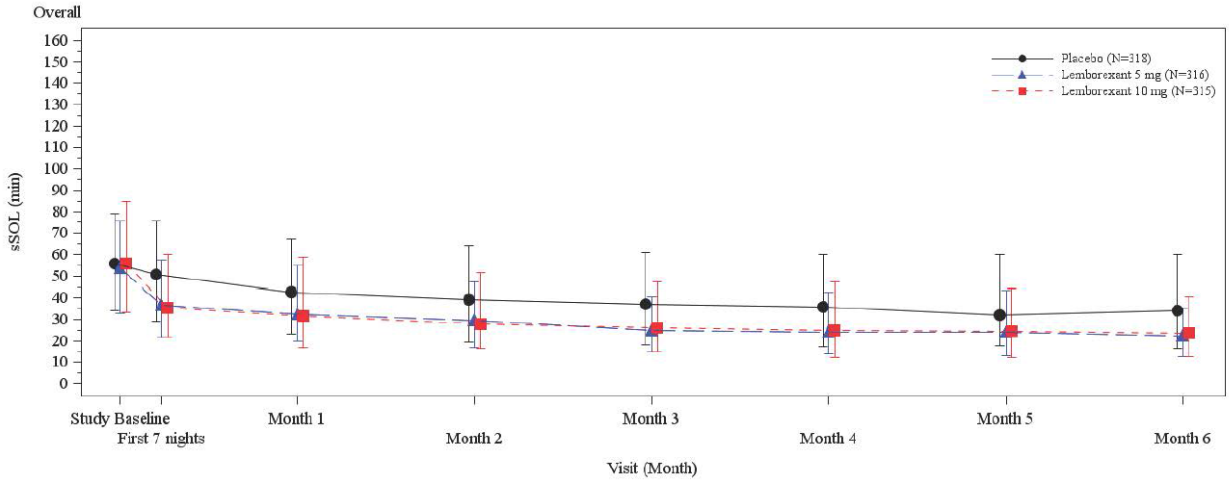
Table 39: Sensitivity Analysis: Jump to Placebo Analysis Results on sSOL (Minutes), Study E2006-G000-303

Treatment Group	# ITT subject	Baseline Geomean Score (SD)	Baseline-Divided LSGM (95% CI)	LSGM Treatment Ratio: Active /Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	318	45.0 (31.8)	0.63 (0.57, 0.70)		
Lemborexant 5 mg	316	43.0 (31.5)	0.48 (0.43, 0.53)	0.76 (0.66, 0.87) 0.0001	Yes
Lemborexant 10 mg	315	45.0 (33.4)	0.47 (0.42, 0.53)	0.74 (0.64, 0.86) 0.0001	Yes

Abbreviations: CI, confidence interview; ITT, intention to treat; LSGM, least squares geometric mean; MCP, multiple comparison procedures; sSOL, subjective sleep onset latency
Note: CI were not adjusted with multiplicity
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

The observed time course of sSOL during the 6 month double blind period is graphically presented in Figure 22. All treatment groups showed a decrease in sSOL score over 6 months, with numerically greater change from baseline for both lemborexant groups at all time points. The two lemborexant groups have the overlapping time course profiles.

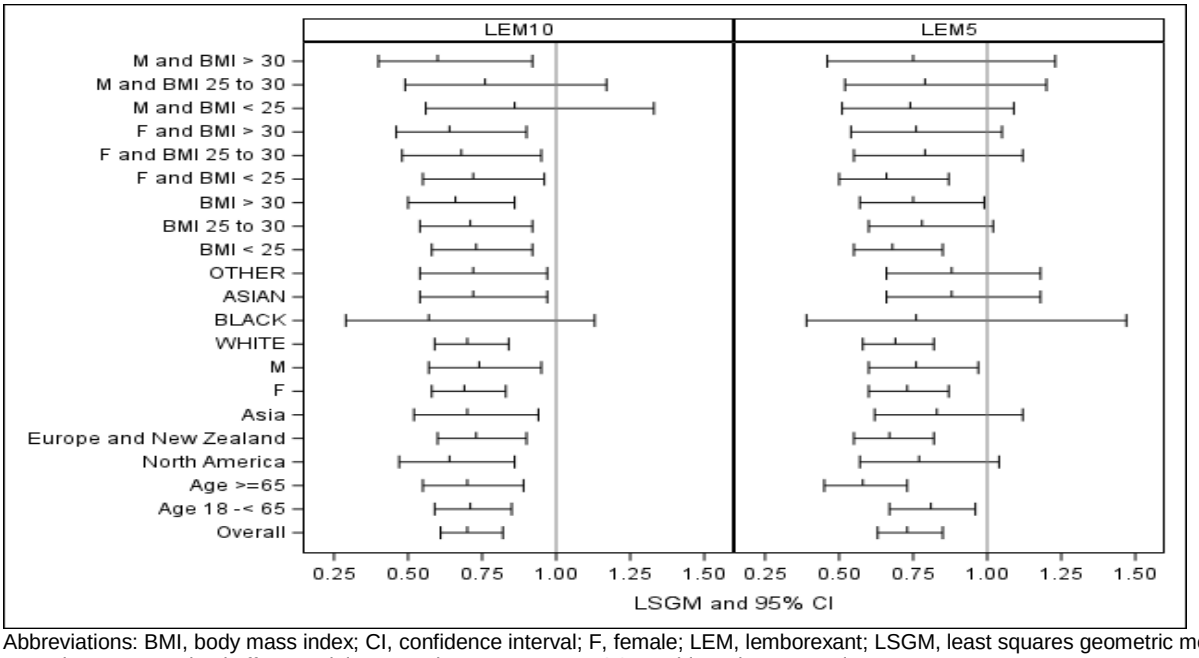
Figure 22: Medians (1st and 3rd Quartiles) sSOL, Study E2006-G000-303



Abbreviation: sSOL, subjective sleep onset latency
Source: Applicant Figure 2 in CSR for Study E2006-G000-303

Further exploratory subgroup analyses on the primary endpoint were assessed by age group, race, gender, baseline BMI, and interaction between gender and baseline BMI. Results are shown in Figure 23. Overall, the subgroups were underpowered to draw conclusions from these findings, but there were no apparent subgroup differences observed in these analyses.

Figure 23: LSGM Treatment Ratio (Active/Placebo) with 95% CI in sSOL by Subgroup, Study E2006-G000-303



Abbreviations: BMI, body mass index; CI, confidence interval; F, female; LEM, lemborexant; LSGM, least squares geometric mean; M, male; MMRM, mixed effect model repeated measurement; sSOL, subject sleep onset latency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)
Based on MMRM Analysis

Data Quality and Integrity

The Applicant reported that Study 303 was organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

8.1.1.8. Efficacy Results – Key Secondary Endpoints

The primary analysis results for the pre-specified key secondary efficacy endpoints according to the hierarchical testing procedure are provided in Table 40 and Table 41. The results on the two key secondary efficacy endpoints are statistically significant for lemborexant 5 mg and 10 mg. Figure 24 and Figure 25 display the histograms of the magnitude of improvement from baseline in sSE and sWASO at Month 6, respectively.

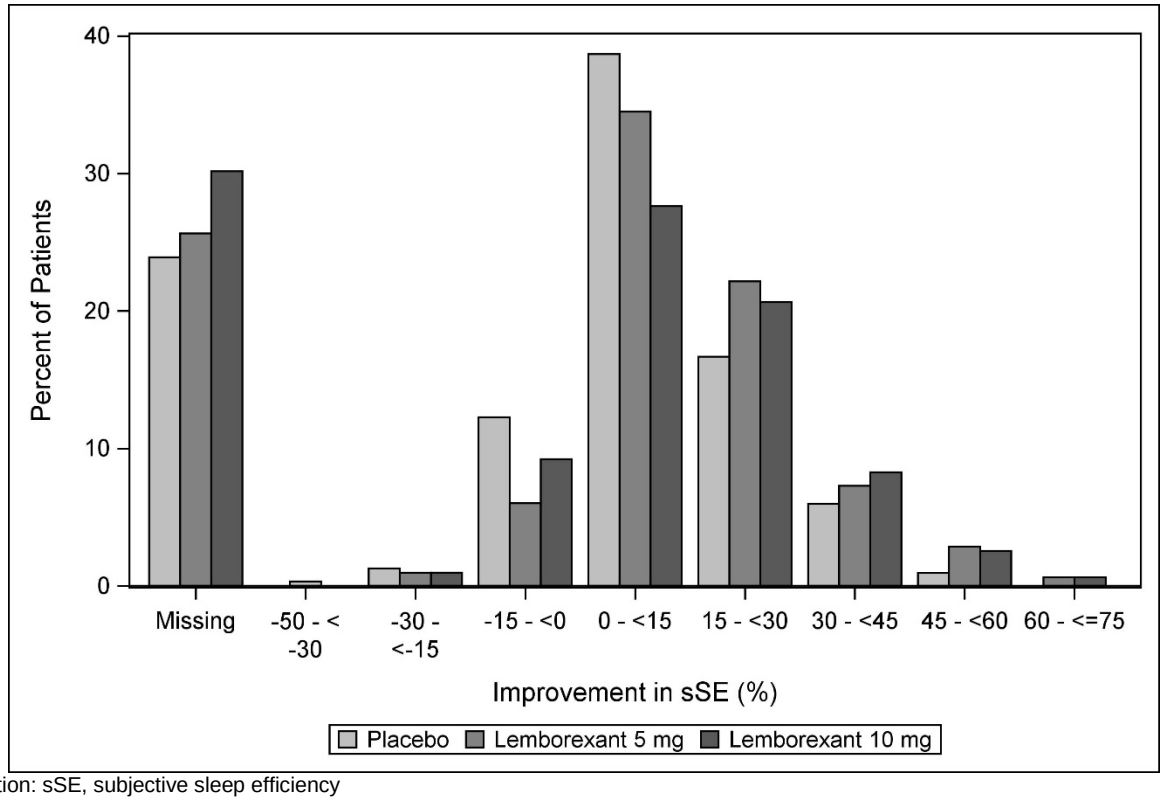
The FDA statistical reviewer performed a sensitivity analysis which utilizes pattern mixture imputation based on jump to placebo. The treatment difference in sSE is 4.2% for lemborexant 5 mg with an unadjusted p-value of 0.0008, 3.8% for lemborexant 10 mg with an unadjusted p-value of 0.001. The treatment difference in sWASO is -15.3 minutes for lemborexant 5 mg with an unadjusted p-value of 0.0019 and -11.7 minutes for lemborexant 10 mg with an unadjusted p-value of 0.0169. The sensitivity analysis results yield the same conclusion as the primary analysis results.

Table 40: Efficacy Results on Key Secondary Endpoint sSE (%), Study E2006-G000-303

Treatment Group	# ITT subject	Baseline Mean (SD)	Month 6 LS Mean (SE)	LS Mean Change from Baseline (95% CI)	LS Mean Treatment Difference: Active-Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	318	61.3 (17.8)	71.4 (0.85)	9.7 (8.1, 11.4)		
Lemborexant 5 mg	316	63.1 (18.2)	75.9 (0.86)	14.2 (12.5, 15.9)	4.5(2.2, 6.9) <0.001	Yes
Lemborexant 10 mg	315	62.0 (17.2)	75.9 (0.86)	14.3 (12.6, 16.0)	4.7 (2.4, 7.0) <0.001	Yes

Abbreviations: CI, confidence interval; ITT, intention to treat; LS, least squares; MCP, multiple comparison procedures; SD, standard deviation; sSE, subjective sleep efficiency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 24: Histogram of the Magnitude of Improvement from Baseline in sSE at Month 6, Study E2006-G000-303



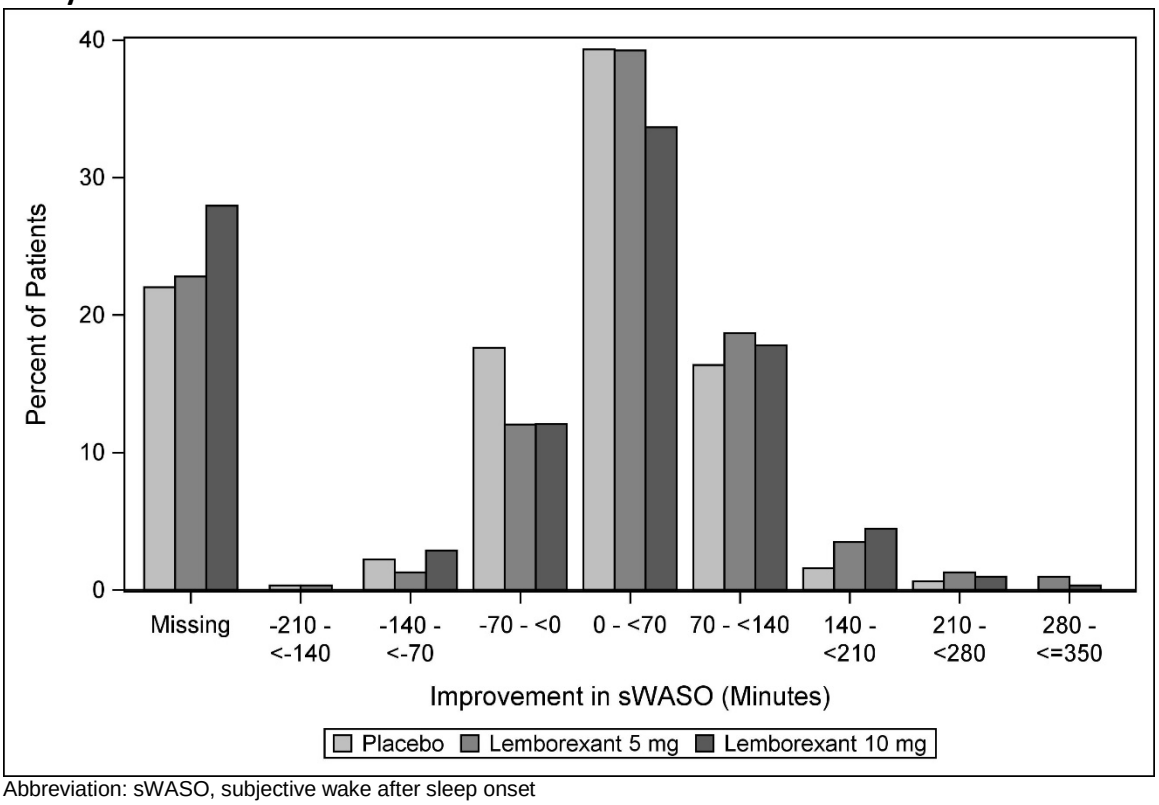
Abbreviation: sSE, subjective sleep efficiency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Table 41: Efficacy Results on Key Secondary Endpoint sWASO (Minutes), Study E2006-G000-303

Treatment Group	# ITT subject	Baseline Mean (SD)	Month 6 LS Mean (SE)	LS Mean Change from Baseline (95% CI)	LS Mean Treatment Difference: Active-Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	318	132.5 (80.2)	105.3 (3.6)	-29.3 (-36.3, -22.2)		
Lemborexant 5 mg	316	132.8 (82.5)	87.9 (3.4)	-46.8 (-53.9, -39.6)	-17.5 (-27.3, -7.6) <0.001	Yes
Lemborexant 10 mg	315	136.8 (87.4)	92.7 (3.7)	-41.9 (-49.2, -34.7)	-12.7 (-22.4, -3.0) 0.011	Yes

Abbreviations: CI, confidence interval; ITT, intention to treat; LS, least squares; MCP, multiple comparison procedures; SD, standard deviation; sWASO, subjective wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 25: Histogram of the Magnitude of Improvement From Baseline in sWASO at Month 6, Study E2006-G000-303



Abbreviation: sWASO, subjective wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Dose/Dose Response

As noted above, improvement with higher doses was not consistently demonstrated for sSE or sWASO at Month 6 (measured as magnitude of improvement from baseline, least mean change from baseline, and placebo-subtracted difference).

Clinical Reviewer Comments*: Increased effectiveness with higher doses is common in drugs used to treat insomnia. However, there was no consistent dose-response for the efficacy of lemborexant in Study 303. The reason for this is unclear; however, a potential reason for not observing a marked dose-response relationship between LEM5 to LEM10 may be explained by the dose-response curve for efficacy (Figure 2 from Section 6.3.2.1.) suggests that LEM10 is marginally higher than LEM5. This is supported by defined magnitudes of changes noted on the histograms that suggested LEM10 may be superior to LEM5 (i.e., dose/response of improvement in 50-<75 minutes sSOL, sWASO 150-<210 minutes).*

Durability of Response

The durability of response over time was measured by change from baseline to end of treatment at 6 months (see Figure 25 above for results) and continued as an extension of Study 303 at 12 months. The study drug appears to maintain effectiveness over time for insomnia disorder (i.e., sSOL continued to demonstrate clinically meaningful results at 1, 2, 3, 4, 5 and 6 months).

In exploratory analyses, the Applicant reported that the larger positive effect on both sleep onset and sleep maintenance parameters with both doses at Months 3 and 6 compared to Month 1 demonstrated that the effect persisted over time. Persistence of effect was defined by the Applicant as present if the mean change from Study Baseline at Month 6 was above the lower bound of the 95% CI at Month 1 for sSE or sTST and below the upper bound of the 95% CI at Month 1 for sSOL and sWASO. Analyses completed for persistence versus loss of effect over duration of exposure (Table 42) were conducted for On-Treatment Full Analysis Set subjects. These analyses compared 1 month of duration of exposure of sSOL, sSE, sWASO and sTST at 3 and 6 months duration of exposure, for (a) LEM Period 1 subjects using the change from Study Baseline. Figure 26 depicts the persistence of effect over 12 months for LEM5 and LEM10 for outcome measures of sSOL, sSE, and sWASO. Although these results are exploratory, the findings suggest that the efficacy of lemborexant persists over times. However, the impact of dropouts on the outcomes was not considered. As such, it is possible that the subjects who did not experience a persistent effect dropped out of the study.

The study design did not measure for effect of the drug after treatment was withheld or stopped.

Table 42: Exploratory Analysis: Persistence vs. Loss of Effect from Month 1 During Phase 1, E2006-G000-303

Endpoint Visit Statistic	Placebo (N=318)	Lemborexant 5 mg (N=316)	Lemborexant 10 mg (N=315)
sSOL			
Month 1			
Change from Study Baseline			
n	299	298	297
LSM visit estimate (95% CI)[a]	-10.50 (-13.78, -7.23)	-19.95 (-23.23, -16.68)	-22.51 (-25.81, -19.21)
Month 2			
Change from Study Baseline			
n	285	286	271
LSM visit estimate (95% CI)[a]	-12.08 (-15.67, -8.49)	-22.94 (-26.53, -19.35)	-25.27 (-28.92, -21.61)
Month 3			
Change from Study Baseline			
n	279	268	264
LSM visit estimate (95% CI)[a]	-13.30 (-17.10, -9.50)	-25.56 (-29.40, -21.72)	-27.06 (-30.94, -23.18)

Endpoint Visit Statistic	Placebo (N=318)	Lemborexant 5 mg (N=316)	Lemborexant 10 mg (N=315)
sSOL			
Month 4			
Change from Study Baseline			
n	269	252	250
LSM visit estimate (95% CI)[a]	-14.63 (-18.36, -10.91)	-25.68 (-29.46, -21.90)	-27.82 (-31.64, -24.01)
Month 5			
Change from Study Baseline			
n	253	244	240
LSM visit estimate (95% CI)[a]	-15.87 (-19.66, -12.08)	-27.09 (-30.92, -23.25)	-28.98 (-32.86, -25.10)
Month 6			
Change from Study Baseline			
n	249	245	229
LSM visit estimate (95% CI)[a]	-16.26 (-20.00, -12.51)	-29.43 (-33.22, -25.65)	-29.51 (-33.37, -25.66)

Source: Listing 16.2.6.1
Subjective Sleep Onset Latency is measured in minutes. Subjective Sleep Efficiency is measured in %. Subjective Wake After Sleep Onset is measured in minutes. Subjective Total Sleep Time is measured in minutes.
sSOL = Subjective Sleep Onset Latency. sWASO = Subjective Wake After Sleep Onset. sSE = Subjective Sleep Efficiency. sTST = Subjective Total Sleep Time. LSM = least squares mean. CI = confidence interval.
a: Based on MMRM model with factors for age group, region, treatment, visit (First 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5 and Month 6), and treatment-by-visit interaction as fixed effects, and the study baseline endpoint as a covariate. Missing values are not imputed and assumed to be missing at random (MAR).
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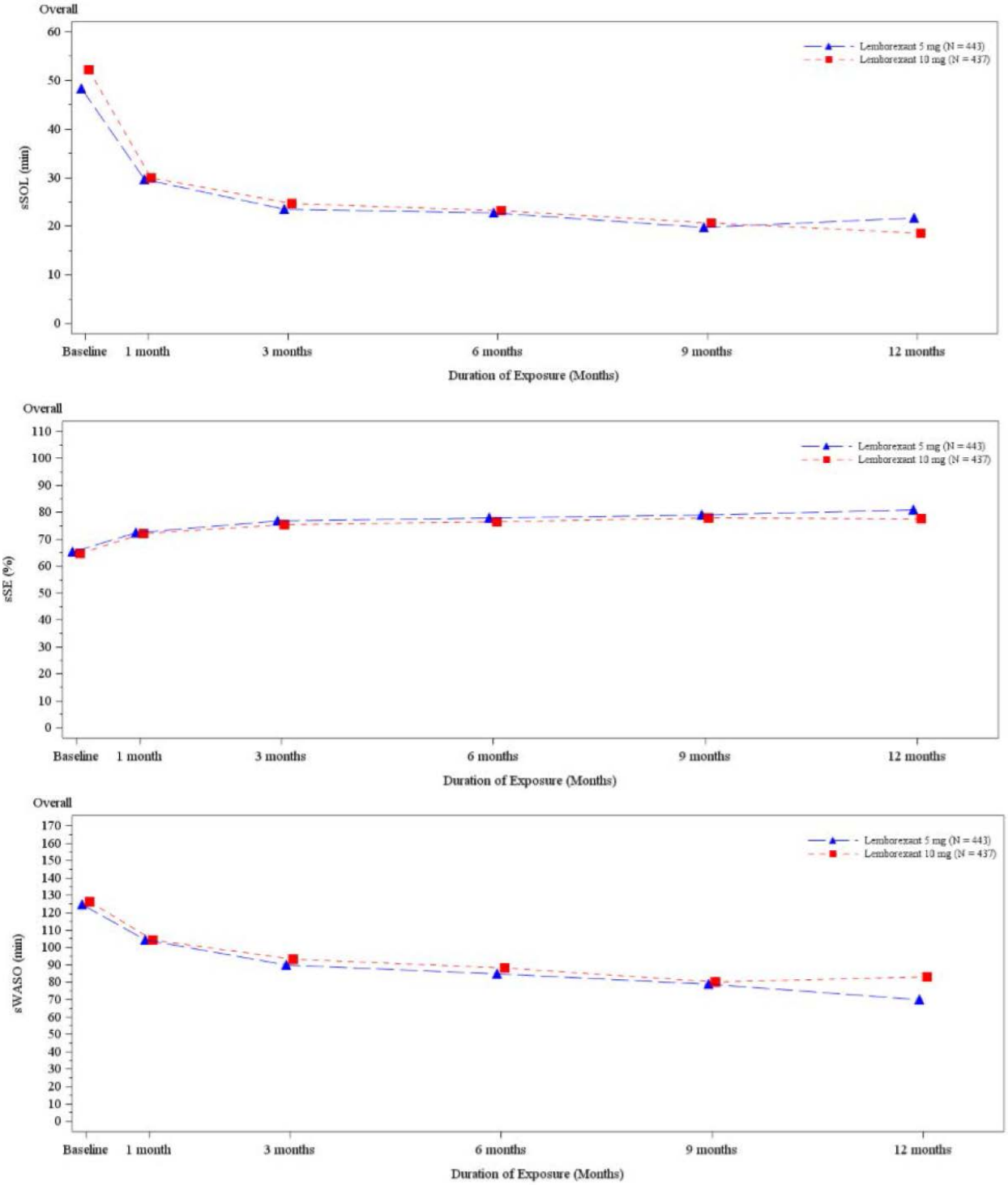
Source: Applicant's Clinical Study Report for E2006-G000-303, Table 17

Figure 26: Exploratory Analysis: Persistence of Effectiveness on sSOL, sSE, and sWASO Over 12 Months of Lemborexant Treatment in Study 303



Abbreviations: sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sWASO, wake after sleep onset
Source: Applicant's Summary of Clinical Efficacy Figure 1.7.3—4,-5,-6

Daily Functioning Score, ISI: For ISI, lower values are better, therefore decreases in values at follow-up visits indicate improvement. At Baseline, mean ISI Daily Functioning Scores were 11.0 in the PBO group, 11.4 in the LEM5 group, and 11.0 in the LEM10 group. At Month 6, mean scores decreased to 6.6 in the PBO group and 5.4 in both the LEM5 and LEM10 groups, mean change from Baseline of -4.3 in the PBO group, -6.0 in the LEM5 group, and -5.7 on the LEM10 group. Treatment differences in the LSM change from Baseline were higher compared to PBO for both LEM5 and LEM10 (P <0.0001 for both comparisons).

Patient Global Impression – Insomnia (PGI-I): The PGI-I, a self-report 4 item assessment, asks subjects' perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, there is no baseline. Compared to PBO, LEM5 and LEM10 had higher effect scores at Month 6 (45.0%, 67.3% and 68.8% of subjects, respectively, p<0.0001), and reduced time to fall asleep (46.1%, 72.8% and 73.1% of subjects, respectively, P<0.0001). In the LEM5 and LEM10 treatment groups, 55.6% and 53.4% of subjects selected that the treatment strength was "just right", compared to 36.0% of subjects in the PBO treatment group (LEM10 comparison with PBO P=0.0073).

8.1.2. E2006-G000-304

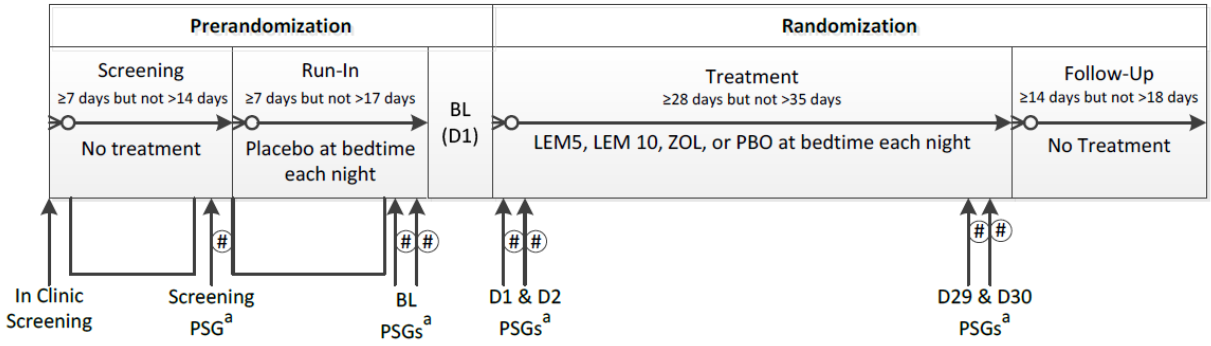
8.1.2.1. Trial Design

This was a global, multicenter, randomized, double-blind, placebo-controlled, active comparator (zolpidem ER), parallel-group study of two dose levels of lemborexant (LEM5 and LEM10) for 30 nights in subjects 55 years or older with insomnia disorder. Subjects were males 65 years or older or females 55 years or older. Approximately 60% of the population was to be age 65 years or older.

Basic Study Design: The study had 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase comprised 3 periods that lasted up to a maximum of 35 days: a Screening Period that included 2 visits; a Run-in Period that began when eligible subjects were dispensed PBO tablets and included 2 consecutive nights during which PSG was recorded, and a Baseline Period that included the Day 1 assessments. The Randomization Phase was comprised of a Treatment Period during which subjects were treated for 30 nights followed by a minimum 14-day interval before an End of Study (EOS) Visit. The Treatment Period began on Day 1 when subjects were randomized in a double-blinded manner, to receive LEM5, LEM10, zolpidem (ZOL), or PBO in a 5:5:5:4 ratio. Randomization was stratified by country and by age group (55 to 64 years; ≥65 years). Study drug was administered and overnight PSGs were initiated on the evenings of Day 1 and Day 2. On Day 29 and Day 30, subjects returned to the clinic for overnight PSGs. Polysomnography was recorded at Baseline, Days 1/2, and Days 29/30.

The study design is presented in Figure 27.

Figure 27: Study Design, E2006-G000-304



= CDR posture and cognitive PAB assessments in the morning following the PSG assessment.
"D" refers to the study day.
BL = baseline, CDR = Cognitive Drug Research, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PAB = performance assessment battery, PBO = placebo, PSG = polysomnography, ZOL = zolpidem tartrate extended release 6.25 mg.
a. All PSG visits required an overnight stay in the clinic. At least 2 nights must have intervened between the second BL PSG and BL (D1).
Source: Applicant's Clinical Study Report, Figure 1

Trial Location: Study E2006-G000-304 was conducted at a total of 88 sites, of which 67 sites had at least one randomized patient (45 sites in the United States, 8 sites in Spain, 6 sites in Germany, 5 sites in Canada, 2 sites in the UK, and 1 site in Italy).

Choice of Control Group: The control group consisted of subjects who meet the inclusion and exclusion criteria for Study 304 and were randomized to the placebo group. The Applicant also included an active comparator group of zolpidem ER. Combined, these groups allow for comparison of lemborexant to no active drug and to one of the most commonly used medications with an FDA indication for insomnia.

Diagnostic Criteria: A medical, psychiatric, and sleep history interview was conducted to determine if the subject met inclusion criteria for insomnia disorder according to DSM-5 criteria and that the subject complained of difficulties with sleep maintenance or early morning awakening, or both.

Screening for other sleep disorders was assessed using the Sleep Disorders Screening Battery (SDSB), consisting of the ESS, the STOP-Bang, the IRLS, and the Munich Parasomnia Scale (MUPS).

Key Inclusion Criteria:

- Males age 65 years or older, or females age 55 years or older meeting DSM-5 diagnostic criteria for Insomnia Disorder

- At screening:
    - History of sWASO typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks, confirmed during run-in period on sleep diary from 7 most recent mornings before the first PSG, such that sWASO ≥60 minutes on at least 3 of the 7 nights
    - Reported regular time in bed sleeping or trying to sleep, between 7 to 9 hours, confirmed using sleep diary (minimum 5 of 7 for eligibility) before the second screening visit
    - Reported habitual bedtime defined as the time the subject attempted to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00, confirmed using Sleep Diary
    - Confirmed sufficient duration of sleep, defined as trying to sleep 7 to 9 hours and a regular bedtime and getting out of bed time, confirmed in completed sleep diary for at least 7 consecutive days during second screening visit and again at baseline visit
    - Screening and study baseline ISI score greater than or equal to 13
- Confirmation During the Run-in Period: Sufficient duration of sleep, defined as trying to sleep 7 to 9 hours and a regular bedtime and getting out of bed time; confirmed completed sleep diary for at least 7 consecutive days during second screening visit and again at baseline visit; Insomnia symptoms (sWASO ≥ 60 minutes) using sleep diary data from the 7 most recent mornings before the PSG;
- Objective PSG evidence of insomnia as follows: WASO average greater than or equal to 60 minutes on the 2 consecutive PSGs, with neither night less than 45 minutes; Confirmed regular bedtime, sufficient duration, and
- Willingness to stay in bed at least 7 hours per night and agreement to not to start other treatments for insomnia during study.

Key Exclusion Criteria:

- Significant current medical diseases, positive for HIV or viral hepatitis, prolonged QTcF (>450 ms), planned surgery, comorbid nocturia, or other clinically significant diseases that might interfere with study assessments
- Symptoms of narcolepsy, complex sleep behavior, sleep-related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, PSG in the past year with elevated hypopnea index, Apnea-Hypopnea Index greater than 15, or Periodic Limb Movement with Arousal Index greater than 15 as measured on the PSG at the second screening visit.
- An exclusionary score on the SDSB as follows: STOPBang (Sleep apnea) score ≥5; IRLS score ≥16; ESS score >15
- BDI-II score >19 at Screening 6, BAI score >15 at Screening; any suicidal ideation with intent

- Nap more than 3X per week, frequent nocturia, excess caffeine use, drug or alcohol abuse/dependence, excessive alcohol consumption, recent insomnia treatment, prohibited medication use, recent cross-time-zone travel, failing suvorexant treatment, woman of childbearing potential.

Clinical Reviewer Comments: *Overall, the enrollment criteria are reasonable, with a few clinical observations. Females were recruited into the study at ages 10 years younger than men. The protocol did not provide justification for the different age criteria for females compared to males. Therefore, the only objective (PSG) phase 3 efficacy data for males in this drug development program were collected in elderly subjects in this study. It would have been preferable if younger males were included in this study for generalizability, because non-elderly males are also part of the target treatment population. Notably, a meta-analysis on insomnia in the elderly reports that total sleep time, sleep efficiency, percentage of slow-wave sleep, percentage of REM sleep, and REM latency all significantly decreased with age, while sleep total sleep time, sleep efficiency, percentage of slow-wave sleep, percentage of REM sleep, and REM latency all significantly decreased with age. Sleep efficiency continues to decrease after age 60 [29]. As such, objective data in a wider range of ages could have been preferable.*

The bedtime routine criteria seem restrictive for the general population or patients with insomnia (e.g., limiting naps, require going to bed between 21:00 and 24:00 every night). However, the restrictions on bedtime routine are considered acceptable because they minimize bias caused by less common sleep patterns (e.g., individuals who work night or swing shifts or take frequent naps were appropriately excluded).

Limiting subjects to only mild symptoms of anxiety and depression also seems to limit real world generalizability because approximately 40 to 50% of adults with insomnia present with a comorbid psychiatric diagnosis, and symptoms of depression, anxiety, and cognitive changes are common (DSM-5, 2014). However, the indication is not associated with any psychiatric or medical diagnoses (i.e., in contrast to the development of lemborexant for ISWRD in Alzheimer's disease), and as such this restriction is reasonable.

Dose Selection: As described for Study 303, the Applicant selected lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10) after completing studies 201 and 107. The dose range used in these studies appears sufficiently broad. The Applicant felt the results of studies 201 and 107 confirmed that LEM5 and LEM10 were the appropriate doses for phase 3 trials.

For the active comparator zolpidem ER, the Applicant chose 6.25 mg, the lower of the two FDA-approved doses. This dose is recommended for women and elderly patients. The Applicant felt this was the better choice because of all of the planned male patients were elderly and the rest of the subjects were female, thus all of the subjects would be limited to 6.25 mg based on labeled dosing strategy. As such, this decision is reasonable.

Clinical Reviewer Comments: *The doses for Study 304 were limited to LEM5 and LEM10. There is a dose-related increase in somnolence, so testing higher doses of lemborexant did not appear necessary as the risks would increase with no expected increase in efficacy. However, lower doses of lemborexant may have been effective and examining the efficacy at lower doses may have been beneficial for some populations, such as elderly subjects.*

Study Treatments: For the test treatment, each subject received study drug for 30 consecutive nights, immediately before the time the subject intended to try to sleep. For the comparator treatment, zolpidem tartrate extended release 6.25 mg (Ambien CR®) was taken orally in tablet form each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep. During PSG studies, the study personnel administered the study drug.

Assignment to Treatment: At Baseline, subjects were randomized in a double-blinded manner to receive LEM5, LEM10, ZOL, or PBO in a 5:5:5:4 ratio. Randomization was stratified by country and by age group (55 to 64 years; ≥65 years). Randomization was based on a computer-generated randomization performed centrally by an interactive voice and web response system (IxRS). The IxRS generated the randomization blister card identification numbers. At Randomization (morning of Day 1), the IxRS assigned each subject a unique 6-digit randomization number.

Blinding: The Run-in period was single blind (only the subject was blinded). During the randomization phase and treatment period, all subjects and personnel were also blinded (double blind). The data were filed with either a contract research organization (CRO) or Applicant and accessible to only key personal until the time of unblinding. The master list was kept in a sealed envelope and maintained with the vender IxRS. The interim analysis results were not provided to the study personnel involved with conduct of the study.

Dose Modification, Dose Discontinuation: No planned modifications of doses were made. This appears appropriate given the objectives of Study 304.

Administrative Structure: The Applicant reported that the study was monitored by qualified personnel from Eisai. Data management was performed by the Eisai Data Management group; statistical analyses were performed by (b) (4), under the supervision of the Biostatistics group at Eisai Inc; population pharmacokinetic (PK)-pharmacodynamic (PD) analyses were performed by the Modeling and Simulations group at Eisai Inc. Serious adverse event reporting and management was handled by (b) (4) and Eisai Pharmacovigilance, and all subject serious adverse event narratives were approved and verified by Eisai Inc. Laboratory tests were performed by (b) (4) PK sample bioanalyses were performed by (b) (4)

Dietary Restrictions: Subjects should have not eaten a meal within 3 hours before taking the study drug. There were no other dietary restrictions in Study 304.

Concurrent Medications: A full list of prohibited medications was provided to the FDA by the Applicant. Prohibited medications included strong and moderate cytochrome P4503A (CYP3A) inhibitors and all CYP3A inducers. Prohibited therapies also included any treatment for insomnia disorder (pharmacologic or non-pharmacologic). Classes of drugs excluded from this study include: sedating anticonvulsants, antihistamines unless non-sedating, sedative anxiolytics, strong and moderate CYP3A inhibitors, CYP3A inducers, melatonin, muscle relaxants, stimulants, and other drugs, e.g., warfarin, heparin, ticlopidine, non-stimulant diet pills, systemic isotretinoin, systemic glucocorticoids and tryptophan.

Any medications (including OTC) or therapy administrated to the subject during the study was recorded on a Prior and Concomitant Medication eCRF or Non Pharmacological Procedures eCRF and details were recorded. If the treatment was related to a previously existing condition, the information was recorded on the Prior and Concomitant Medication eCRF or Non Pharmacological Procedures eCRF.

Rescue Medications: No other treatments were permitted for insomnia disorder and no other treatments were offered for subjects who did not respond to their treatment.

Treatment Compliance, Subject Completion, Continuation, Withdrawal: Compliance was assessed for each study drug by examination of blister packs returned to the investigator at the end of the Run-in and Treatment Periods. Compliance was calculated as number of pills dispensed minus number of pills returned, taking into account the number of pills that should have been returned. If a subject either lost or failed to return the study drug kit at the end of study, and was in the early part of the allowed visit window, the compliance calculation result suggested that subjects had "taken" more pills than expected.

Clinical Reviewer Comments*: Neither rescue medications nor other treatments for insomnia were permitted in the lemborexant drug development program. Although excluding rescue medications for insomnia disorder limits generalizability to real-world clinical settings, such exclusions are considered reasonable because other medications may confound the assessment of efficacy or safety. However, providing no treatment for one month may be a burden for patients with impairing insomnia disorder.*

Several categories of medications were on list of prohibited concomitant medications. However, the choices were inconsistent. For example, several categories of drugs that cause sedation or increased alertness were not excluded (e.g., sedating or alerting antidepressants, sedating antipsychotics, and "non-sedating" antihistamines). As such, subjects could be using these medications to improve sleep or increase alertness, and it would not have been prohibited at baseline or during the study. This choice could influence efficacy data. However, the possible effect is likely to be equal across lemborexant and placebo treatment arms.

8.1.2.2. Study Endpoints

Primary endpoint: The primary efficacy endpoint was the change from baseline (CFB) for mean log(LPS) on Days 29/30 (i.e., the last two nights of 1 month of treatment of LEM10 and LEM5 compared to PBO). The change from baseline to end of treatment in LPS, as measured by PSG, has been used to demonstrate the efficacy of multiple drugs previously approved for the treatment of insomnia.

There were three prespecified key secondary endpoints: CFB for mean SE on Days 29/30 of LEM10 and LEM5 compared to PBO, CFB for mean WASO on Day s 29/30 of LEM10 and LEM5 compared to PBO, and CFB for mean wake after sleep onset in the second half of the night (WASO2H) on Days 29/30 of LEM10 and LEM5 compared to ZOL.

Table 43: Applicant's Definition of Sleep Parameters for Study E2006-G000-304

Abbreviation	PSG Sleep Parameter	Applicant Definition
LPS	Latency to Persistent Sleep	Minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
SE	Sleep Efficiency	Proportion of time spent asleep per TIB, calculated as TST/interval from lights off until lights on
TST	Total Sleep Time	Minutes of sleep from sleep onset until terminal awakening
WASO	Wake After Sleep Onset	Minutes of wake from the onset of persistent sleep until lights on
WASO2H:	Wake After Sleep Onset, second half of the night	Minutes of wake during the interval from 240 minutes after lights off until lights on

Abbreviations: LPS, latency to persistence sleep; PSG, polysomnography; SE, sleep efficiency; TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset
Source: Clinical Reviewer generated table summarized from Study 304 Clinical Study Report

Assessment schedule: The Applicant's trial of schedule of events for study E2006-G000-304 is presented in Table 44.

Table 44: Applicant's Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	**Prerandomization**								**Randomization**											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-14/+4	-3/+4		-3/+3		-3/+3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-35 to -17	-17 to -10	-16 to -9	-10 to -4	-9 am to -3 am	-9 pm to -3 pm	-8 to -2	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/Assessments																				
Demographics	X																			
Informed consent	X																			
Inclusion/exclusion criteria[f]	----------→																			
Height	X																			
Weight	X							X								X		X	X	
Clinical laboratory tests	X							X								X		X	X	X
Viral screening[g]	X																			
Vital signs	X							X								X		X	X	X
12-lead ECG	X							X								X		X	X	X
Sleep, medical, and psychiatric history	X																			
ISI	X			X				X								X				
SDSB[h]	X																			
Physical examination[i]	X															X		X	X	X
Prior/concomitant medications	----------→																			
Beck Depression Inventory II	X																			
Beck Anxiety Inventory	X																			
Urine drug test	X	X		X		X		X			X		X		X					X
Postural stability		X	X		X		X			X		X		X		X				
Cognitive PAB		X	X		X		X			X		X		X		X				
FSS	X			X				X								X				
Morning Sleepiness			X		X		X			X		X		X		X				
Sleep Diary	----------→																			

Phase	**Prerandomization**								**Randomization**											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-14/+4	-3/+4		-3/+3		-3/+3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-35 to -17	-17 to -10	-16 to -9	-10 to -4	-9 am to -3 am	-9 pm to -3 pm	-8 to -2	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
EQ-5D-3L	X			X				X								X				
PK blood sampling											X	X			X	X				X
eC-SSRS	X							X				X				X		X	X	X
Polysomnography			X		X		X			X		X		X		X				
Randomization									X											
PGI-Insomnia																X				
T-BWSQ																		X	X	
Dispense study drug			X									X								
Study drug at bedtime	----------→																			
Retrieve unused study drug								X					X							
Check study drug compliance				X				X					X							
Admission to clinic		X		X		X		X			X		X		X					
Discharge from clinic			X		X		X			X		X		X		X				
Discharge from study																		X	X	

Abbreviations: BL, baseline; CDR, Cognitive Drug Research; eC-SSRS, electronic Columbia-Suicide Severity Rating Scale; EMG, electromyography; EOS, end of study; ET, early termination; FSS, Fatigue Severity Scale; ISI, Insomnia Severity Index; PAB, performance assessment battery; PGI, Patient Global Impression; PK, pharmacokinetic; PSG, polysomnography; SDSB, Sleep Disorders Screening Battery; T-BWSQ, Tyrer Benzodiazepine Withdrawl Symptom Questionnaire; UN, unscheduled visit

[a] Must have been consecutive with Visit 3a.
[b] Must have been consecutive with Visit 5b.
[c] Must have been consecutive with Visit 7a.
[d] Must have occurred 14 – 18 days after Visit 8.
[e] Subjects who discontinued the study early for any reason after Randomization at Visit 5 should have competed this visit.
[f] Inclusion and exclusion criteria that were to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2 of the protocol.
[g] Viral screening for hepatitis B and hepatitis C was conducted.
[h] The Sleep Disorders Screening Battery included: STOPBang Sleep Apnea Questionnaire, International Restless Legs Scale, Epworth Sleepiness Scale, and Munich Parasomnia Scale.
[i] Full physical examination (including a brief neurological examination) was carried out at Screening and EOS and ET (if applicable). Brief physical examinations were carried out at other visits.
[j] For training purposes only. Introduction to the CDR posture assessment and at least 2 training sessions of cognitive PAB were to be completed before the end of Visit 2a.
Source: Applicant's Clinical Study Report E2006-G000-304, Table 4

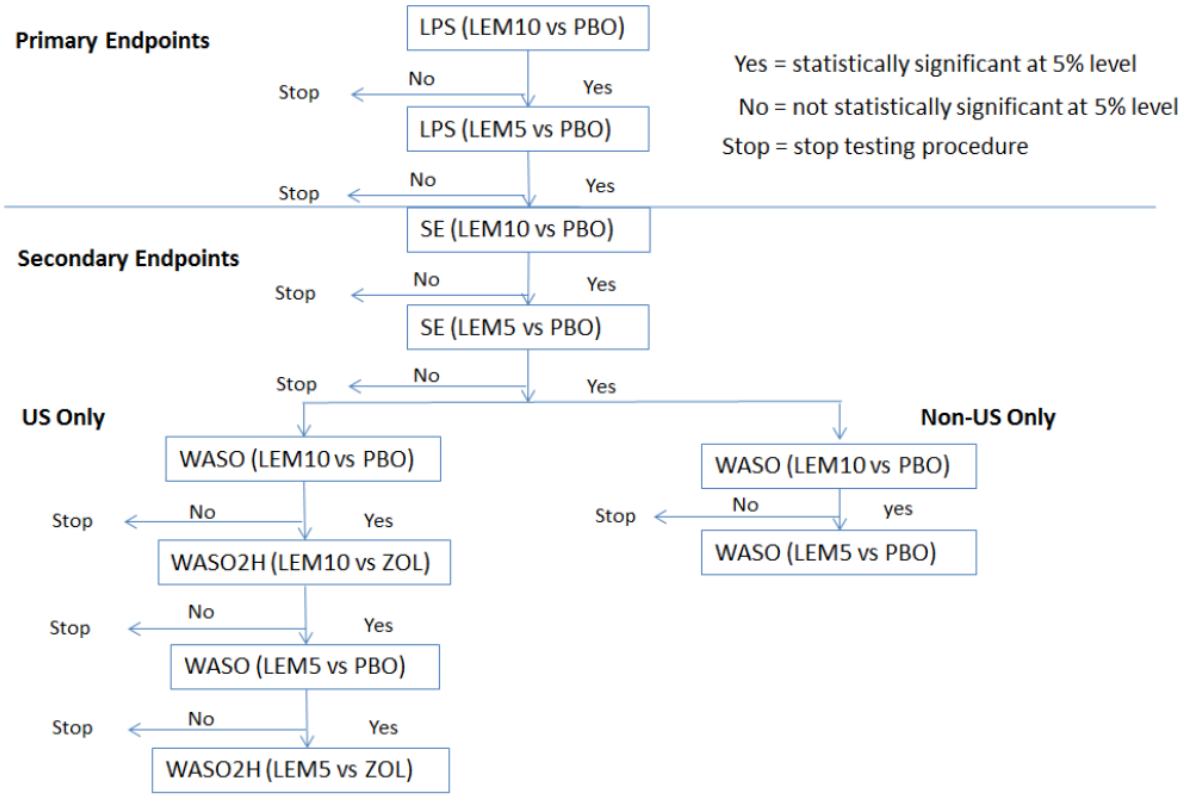
8.1.2.3. Statistical Analysis Plan

The statistical analysis plan was finalized before the data were unblinded. At the pre-NDA meeting held on June 14, 2018, the Agency raised concerns about the proposed primary analysis method which was based on missing data imputation using a CCMC assumption. The Agency also raised concerns on the interpretability of Eisai's proposed TPA. The Applicant agreed to amended statistical analysis plan with the details of the revised TPA. The Applicant submitted the results of the original TPA and presented the revised TPA as a post hoc analysis in the integrated summary of efficacy.

The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement. The change from baseline of log(LPS), SE, WASO2H, and WASO on Days 1/2 and Days 29/30 was analyzed using the mixed effect model repeated measurement analysis (MMRM) with factors of age group (55 to 64, and ≥ 65 years old), region (North America and Europe), treatment, visit (Days 1/2 and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline as a covariate based on FAS. Because the Applicant considered LPS to be non-normally distributed and the Agency had no evidence to counter that assumption, a log-transformation would be used in the primary analysis. The distribution of the LPS would be explored. In the case of log transformation, statistical comparisons were conducted using the least squares geometric means (LSGM). The unstructured covariance matrix (UN) was used in the analysis. In the case of non-convergence of UN, the autoregressive [AR(1)] covariance matrix were used in the model. Before the implementation of the MMRM model, the missing values were imputed using pattern-mixture model multiple imputation assuming the missing values are missing not at random utilizing the complete case missing value pattern (CCMV - subjects who completed primary efficacy assessments without missing values).

A sequential gate-keeping procedure was used for the primary and the key secondary endpoint comparisons to control for the overall type I error at the 0.05 significance level. The first endpoint comparisons were tested at the 0.05 significance level. The sequence was as follows: if the testing was found to be statistically significant, then proceed to the next endpoint testing at significance level of 0.05, otherwise stop testing. The gate-keeping testing procedure of the primary and secondary endpoints is illustrated in Figure 28.

Figure 28: Flow Chart of Gate-Keeping Testing Procedure



Abbreviations: LEM, lemborexant; LPS, latency to persistence sleep; PBO, placebo; SE, sleep efficiency; WASO wake after sleep onset; ZOL, zolpidem
Source: Applicant's Clinical Study Report, Figure 2

The following supportive or sensitivity analyses were performed on the primary endpoint and the key secondary endpoints: per protocol (PP) analysis (primary analysis on PP analysis set), completer analysis (primary analysis on completers), as-treated analysis (the primary analysis based on the actual treatment received, MMRM analysis without imputation, MMRM analysis with MI imputation assuming CCMV-4, and tipping point analysis.

An interim analysis was planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) had been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis was conducted for administrative reasons as detailed in the separate Interim Analysis Charter (which is included as an Appendix of the SAP). The interim analysis was limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. The study was not planned to be terminated for either futility or efficacy. Therefore no adjustment to the type I error rate was planned.

Protocol Amendments

The original protocol was dated March 21, 2016 and was revised six times including four protocol amendments. Table 45 highlights protocol changes made for Study E2006-G000-304.

Table 45: Applicant Reported Revisions/Amendments to the Protocol for Study E2006-G000-304

Date	Key Changes
4/4/2016	• Specified additional secondary endpoints/objectives 1) Determination of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL with respect to SE, WASO, TST, sSOL, sSE, sWASO, and sTST at defined time intervals; 2) Whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL with respect to LPS, ISI, FSS, cognitive performance the morning after the first 2 nights of treatment, the proportions of sleep onset and sleep maintenance responders as defined by LPS, WASO, sSOL, and sWASO
6/24/2016	• Exclusion criteria include current diagnosis of obstructive sleep apnea. • Revised STOPBang score, Epworth Sleepiness Scale score cutoff for exclusion from study. • Prohibited strong CYP3A inhibitors from being used any time during study, even if intermittently. • Added sleep onset latency as a PSG variable. • Allowed flexibility for the means of documenting the time and date of 2 most recent doses before each blood sample for PK • Moved analysis of cognitive PAB tasks from exploratory to secondary analyses. • Deleted glucose-metabolizing agents from list of prohibited/concomitant medications.
2/16/2017	• Revised approximate number of sites from 90 to 105. • Revised to Screening Period from up to -28 days to up to -35 days. • Revised total number of expected screened subjects from 2100 to 2800. • Revised inclusion and exclusion criteria. • Revised analyses for Rebound Insomnia. • Added the requirement for monitoring of seizures and falls. • Revised T-BWSQ assessment description such that scores above 20 would not be considered clinically significant and that the symptoms would no longer be summarized separately from all other AEs.
6/16/2017	• Revised order of primary, key secondary, additional secondary, and exploratory objectives and related endpoints. • Revised process for control of type I error. • Added WASO1H as a sleep architecture parameter (efficacy). • Revised age groups for analysis.
2/5/2018	• Revised order of key secondary objectives and related endpoints • Added sensitivity analysis • Revised process for control of type I error • Revised age ranges for categorical variables

Abbreviations: AE, adverse event; FSS, Fatigue Severity Scale; ISI, Insomnia Severity Index; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LPS, latency to persistent sleep; PAB, performance assessment battery; PBO, placebo; PK, pharmacokinetics; PSG, polysomnography; SE, sleep efficiency; sSE, subject sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO. subjective wake after sleep onset; T-BWSQ. Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; TST, total sleep time; WASO, wake after sleep onset; WASO1H, wake after sleep onset in the first half of the night; ZOL, zolpidem extended release 6.25 mg

Source: Modified from Applicant's Appendix 16.1.1. and Applicant Table 6 in the Clinical Study Report for E2006-G000-304

8.1.2.4. Study Results for E2006-G000-304

Compliance with Good Clinical Practices
The Applicant reports that study was performed in full compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is reportedly archived as required by regulatory authorities.

Financial Disclosure

The Applicant submitted the expected financial certification and disclosure statement, per 21 CFR 314.50(k), for all clinical investigators who participated in Study E2006-G000-304, as agreed with the Division at the Type B pre-NDA meeting. For Study 304, one investigator was listed as receiving Significant Payment of Other Sorts: (b) (6) (b) (6) is the (b) (6) for study E2006-G000-304 and at site (b) (6) where (b) (6) enrolled (b) (6) subjects. Total disclosure amount is $44,733.20.

Patient Disposition
A total of 3537 subjects signed informed consent for entry into the study. Of these, 2531 (71.6%) subjects were screening failures, 1436 (40.6%) subjects continued into the Run-in Period, and 1006 (28.4%) continued into the Treatment Period. The main reasons for screening failure were subjects not meeting inclusion/exclusion criteria (2302 [65.1%] subjects) followed by withdrawal of consent (154 [4.4%] subjects).

A total of 1006 subjects were randomized (269 in LEM10, 266 in LEM5, 263 in ZOL, 208 in PBO). All randomized subjects were treated with study drug. The majority (n=962, 95.6%) of randomized subjects completed the study. All 1006 subjects were included in the planned analyses.

Table 46: Subject Disposition and Reasons for Discontinuation from Study 304

	Placebo	Zolpidem ER 6.25 mg	Lemborexant		
			5 mg	10 mg	Total
Randomized, n	208	263	266	269	535
Not treated, n (%)	0	0	0	0	0
Treated, n (%)	208 (100)	263 (100)	266 (100)	269 (100)	535 (100)
Completed the study, n (%)	198 (95.2)	246 (93.5)	258 (97.0)	260 (96.7)	518 (96.8)
Discontinued from the study, n (%)	10 (4.8)	17 (6.5)	8 (3.0)	9 (3.3)	17 (3.2)
Primary reason(s) for discontinuation[a], n (%)	10 (4.8)	17 (6.5)	8 (3.0)	9 (3.3)	17 (3.2)
Adverse event[b]	2 (1.0)	6 (2.3)	2 (0.8)	3 (1.1)	5 (0.9)
Lost to follow-up	2 (1.0)	1 (0.4)	1 (0.4)	0	1 (0.2)
Subject choice	2 (1.0)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Inadequate therapeutic effect	1 (0.5)	0	0	0	0
Withdrawal of consent	2 (1.0)	3 (1.1)	1 (0.4)	2 (0.7)	3 (0.6)
Other	1 (0.5)	6 (2.3)	2 (0.8)	3 (1.1)	5 (0.9)
Other reason(s) for discontinuation[a], n (%)	1 (0.5)	3 (1.1)	0	0	0
Adverse event[b]	0	1 (0.4)[c]	0	0	0
Subject choice	1 (0.5)	1 (0.4)	0	0	0
Inadequate therapeutic effect	0	0	0	0	0
Other	0	1 (0.4)	0	0	0

Percentages are based on the number of subjects randomized in the relevant treatment group. AE = adverse event, CRF = case report form, ER = extended release.
a: As reported on the Subject Disposition CRF. Multiple 'other' reasons for discontinuation may have been checked on the CRF, therefore, percentages may add up to more than the overall percentage of subjects who discontinued.
b: Corresponding AEs leading to withdrawal from the study or study drug were reported on the AE CRF.
c: Adverse event is not included under primary reasons for discontinuation, subcategory adverse event.
Source: Table 14.1.1.3.

Source: Applicant's Table 7 of CSR of Study 304.

Clinical Reviewer Comments: *The overall dropout rate was low for Study 304 (3 to 6.5% across the treatment groups), which is preferred in clinical trials. The discontinuation rates were lower in the LEM5 and LEM10 groups than the placebo or zolpidem groups. The zolpidem group had a higher incidence of discontinuation due to adverse events, suggesting it may not be tolerated as well as placebo or LEM.*

8.1.2.5. Protocol Violations/Deviations

Protocol deviations were identified, reviewed, and documented by the Applicant's clinical team prior to database lock/treatment unblinding. All protocol deviations were categorized as major/minor and by standard classifications including violations of inclusion/exclusion criteria, noncompliance with or incorrect implementation of protocol procedures, noncompliance of study drugs/dosage intervention, use of prohibited concomitant medication.

A total of 114 (11.3%) subjects had one or more major protocol deviations, with generally similar rates across treatment groups. The most common major protocol deviations (in >1% of subjects) were inclusion criteria (38 [3.8%] subjects), study procedures/assessments (36 [3.6%] subjects), study drug administration/dispense (26 [2.6%] subjects), and exclusion criteria (19 [1.9%] subjects). Table 47 summarizes the major protocol deviations for Study 304.

Clinical Reviewer Comments*: The reported deviations seem approximately balanced across the treatment groups and occurred at a relatively low frequency and are not expected to have a significant impact on interpretation of efficacy results in Study 304.*

Table 47: Major Protocol Deviations for Study E2006-G000-304, Full Analysis Set

			Lemborexant			
Category	Placebo (N=208) n (%)	Zolpidem ER 6.25 mg (N=263) n (%)	5 mg (N=266) n (%)	10 mg (N=269) n (%)	Total (N=535) n (%)	Combined Total (N=1006) n (%)
Subjects with any major protocol deviations	26 (12.5)	24 (9.1)	32 (12.0)	32 (11.9)	64 (12.0)	114 (11.3)
Concomitant Medication	0	1 (0.4)	0	2 (0.7)	2 (0.4)	3 (0.3)
Exclusion Criteria	2 (1.0)	4 (1.5)	4 (1.5)	9 (3.3)	13 (2.4)	19 (1.9)
Inclusion Criteria	6 (2.9)	10 (3.8)	13 (4.9)	9 (3.3)	22 (4.1)	38 (3.8)
Other Protocol Deviation	0	0	1 (0.4)	0	1 (0.2)	1 (0.1)
Safety Reporting	0	0	1 (0.4)	0	1 (0.2)	1 (0.1)
Study Procedures/Assessments	11 (5.3)	7 (2.7)	8 (3.0)	10 (3.7)	18 (3.4)	36 (3.6)
Study Treatment Admin/Dispense	9 (4.3)	3 (1.1)	7 (2.6)	7 (2.6)	14 (2.6)	26 (2.6)
Study Treatment Compliance	0	0	1 (0.4)	0	1 (0.2)	1 (0.1)
Visit Scheduling	0	0	0	2 (0.7)	2 (0.4)	2 (0.2)

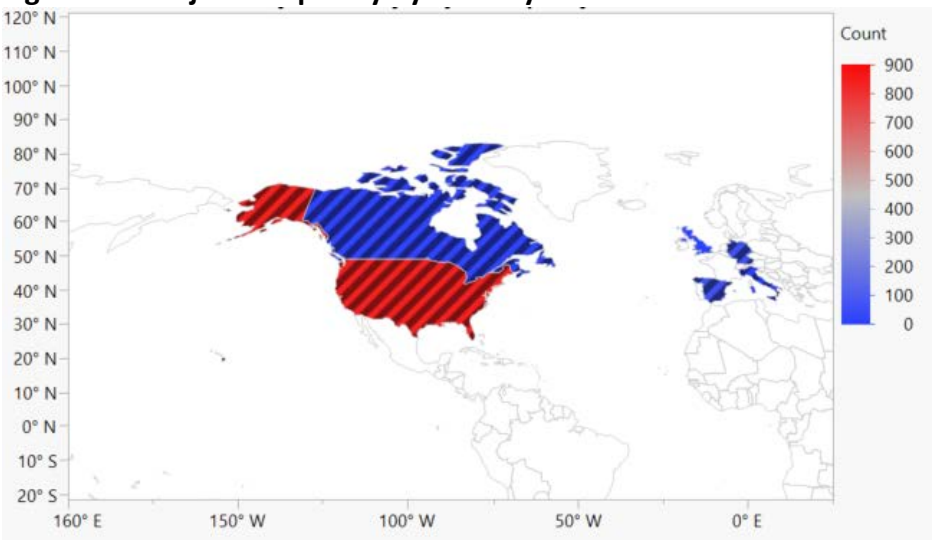
Abbreviation: ER, extended release
Source: Applicant's Table 14.1.2, Clinical Study Protocol for E2006-G000-304

There were three instances of prohibited concomitant medication usage that were considered major protocol deviations. Two deviations were recorded as taking a medication, but the name of the medication wasn't listed, so it is unclear what effect this would have. Subject (b) (6) tested positive for taking Benadryl. Although timing, dose, and reason for taking the medication were not described, this subject was in the zolpidem group, and therefore the results do not influence the efficacy outcomes for lemborexant compared to placebo.

8.1.2.6. Demographic Characteristics for E2006-G000-304

The trial was conducted at a total of 88 sites, at which 67 sites had at least one randomized patient (45 sites in the United States, 8 sites in Spain, 6 sites in Germany, 5 sites in Canada, 2 sites in the UK, and 1 site in Italy). Figure 29 highlights the frequency of subjects by country.

Figure 29: Subject Frequency by Country



Source: Clinical Reviewer generated figure from E2006-G000-304 study data (adsl.xpt)

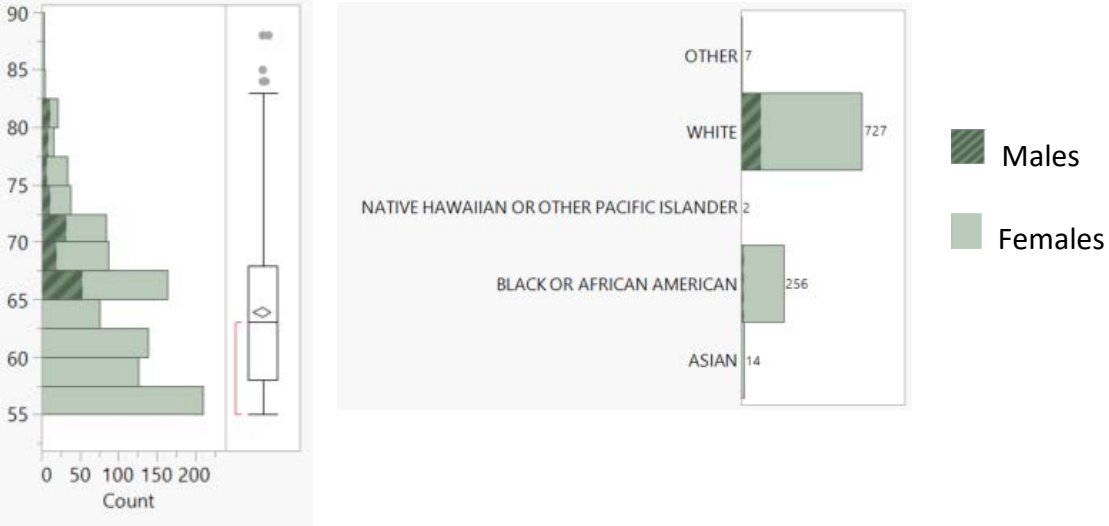
The majority of subjects were female (86.4%) and white (72.3%). The overall median age was 63.9 years (range: 55 to 88 years). In general, demographic and baseline characteristics were similar across treatment groups. Table 48 reviews the demography of Study 304. Figure 30 displays the distribution of subjects by age, race, and sex.

Table 48: Demographic Characteristics of the Primary Efficacy Analysis for Study 304

Demographic Parameters	Placebo (N=208)	Zolpidem ER 6.25 mg (N=263)	Lemborexant 5 mg (N=266)	Lemborexant 10 mg (N=269)	Total (N=1006)
Sex					
Male	24 (11.5)	37 (14.1)	37 (13.9)	39 (14.5)	137 (13.6)
Female	184 (88.5)	226 (85.9)	229 (86.1)	230 (85.5)	869 (86.4)
Age					
Mean years (SD)	63.4 (6.36)	64.3 (7.12)	63.7 (6.78)	64.2 (6.88)	63.9 (6.81)
Median (years)	62.0	63.0	63.0	64.0	63.0
Min, max (years)	55, 82	55, 83	55, 88	55, 85	55, 88
Age Group					
< 65 years	115 (55.3)	143 (54.4)	148 (55.6)	147 (54.6)	553 (55.0)
≥ 65 years	93 (44.7)	120 (45.6)	118 (44.4)	122 (45.4)	453 (45.0)
Race					
White	153 (73.6)	173 (65.8)	199 (74.8)	202 (75.1)	727 (72.3)
Black or African American	51 (24.5)	80 (30.4)	63 (23.7)	62 (23.0)	256 (25.4)
Asian	2 (1.0)	5 (1.9)	2 (0.8)	5 (1.9)	14 (1.4)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	2 (0.8)	0	0	2 (0.2)
Other[1]	2 (1.0)	3 (1.1)	2 (0.8)	0	7 (0.7)
Ethnicity					
Hispanic or Latino	35 (16.8)	32 (12.2)	51 (19.2)	47 (17.5)	165 (16.4)
Not Hispanic or Latino	173 (83.2)	231 (87.8)	215 (80.8)	222 (82.5)	841 (83.6)
Region					
North America	180 (86.5)	226 (85.9)	226 (85.0)	231 (85.9)	863 (85.8)
Europe	28 (13.5)	37 (14.1)	40 (15.0)	38 (14.1)	141 (14.2)

Abbreviations: ER, extended release; SD, standard deviation
Source: Biostatistics Reviewer's Analysis (adsl.xpt)

Figure 30: Distribution of Age, Race, and Sex in Study E2006-G000-304



Source: Clinical Reviewer figure created from E2006-G000-304 data (adsl.xpt)

Other Baseline Characteristics (e.g., weight, height, BMI, sleep parameters) are described in Table 49.

Table 49: Other Baseline Characteristics in Study E2006-G000-304, Full Analysis Set

			Lemborexant			
Category	Placebo (N=208)	Zolpidem ER 6.25 mg (N=263)	5 mg (N=266)	10 mg (N=269)	Total (N=535)	Combined Total (N=1006)
Weight (kg)						
n	208	263	266	269	535	1006
Mean (SD)	73.94 (15.073)	73.70 (13.530)	73.66 (14.724)	73.24 (13.505)	73.45 (14.113)	73.62 (14.156)
Median	72.55	72.00	72.80	71.50	72.30	72.30
Min, Max	43, 129.6	46, 123.4	43, 132.9	47.6, 117	43, 132.9	43, 132.9
Height (cm)						
n	208	263	266	269	535	1006
Mean (SD)	163.98 (7.647)	163.86 (7.650)	163.65 (8.404)	163.78 (8.422)	163.72 (8.406)	163.81 (8.053)
Median	162.60	163.00	162.60	162.60	162.60	162.60
Min, Max	146, 187.9	144.8, 185.7	143, 190	144.8, 191.5	143, 191.5	143, 191.5
BMI (kg/m^2)						
n	208	263	266	269	535	1006
Mean (SD)	27.47 (5.134)	27.42 (4.609)	27.44 (4.741)	27.29 (4.553)	27.36 (4.644)	27.40 (4.736)
Median	26.57	27.21	26.82	26.92	26.87	26.96
Min, Max	17.1, 49.1	18.1, 54.6	17.4, 41.8	17.6, 47.2	17.4, 47.2	17.1, 54.6

			Lemborexant			
Category	Placebo (N=208)	Zolpidem ER 6.25 mg (N=263)	5 mg (N=266)	10 mg (N=269)	Total (N=535)	Combined Total (N=1006)
BMI (kg/m^2) group, n (%)						
<18.5	1 (0.5)	1 (0.4)	3 (1.1)	2 (0.7)	5 (0.9)	7 (0.7)
18.5 to <25	76 (36.5)	80 (30.4)	86 (32.3)	81 (30.1)	167 (31.2)	323 (32.1)
25 to 30	73 (35.1)	127 (48.3)	103 (38.7)	126 (46.8)	229 (42.8)	429 (42.6)
>30	58 (27.9)	55 (20.9)	74 (27.8)	60 (22.3)	134 (25.0)	247 (24.6)
LPS (minutes)						
n	208	262	266	269	535	1005
Mean (SD)	43.89 (33.596)	44.52 (38.349)	44.86 (36.528)	44.61 (32.986)	44.73 (34.760)	44.50 (35.465)
Median	33.63	31.50	33.13	38.50	35.75	34.25
Min, Max	2.5, 267.0	0.5, 205.0	2.3, 264.0	2.0, 193.8	2.0, 264.0	0.5, 267.0
WASO (minutes)						
n	208	262	266	269	535	1005
Mean (SD)	111.75 (37.179)	114.31 (39.922)	113.44 (38.953)	114.83 (39.997)	114.13 (39.451)	113.69 (39.091)
Median	105.88	107.25	105.50	107.50	106.25	106.25
Min, Max	60.0, 280.0	43.5, 286.8	60.3, 251.0	37.3, 249.5	37.3, 251.0	37.3, 286.8
TST (minutes)						
n	208	262	266	269	535	1005
Mean (SD)	330.67 (46.268)	326.99 (54.852)	328.00 (54.224)	325.07 (52.819)	326.53 (53.492)	327.50 (52.422)
Median	338.13	335.0	337.88	330.50	335.00	335.75
Min, Max	166.0, 410.0	96.5, 416.5	112.5, 414.3	160.5, 412.0	112.5, 414.3	96.5, 416.5
SE (%)						
n	208	262	266	269	535	1005
Mean (SD)	68.89 (9.639)	68.13 (11.419)	68.36 (11.268)	67.85 (10.849)	68.10 (11.052)	68.27 (10.868)
Median	70.44	69.79	70.39	69.01	69.79	70.05
Min, Max	34.6, 85.4	20.1, 86.8	23.4, 86.3	34.0, 85.8	23.4, 86.3	20.1, 86.8
WASO2H (minutes)						
n	208	262	266	269	535	1005
Mean (SD)	74.44 (30.109)	78.04 (33.849)	76.60 (32.903)	76.88 (32.126)	76.74 (32.484)	76.60 (32.366)
Median	67.13	70.00	71.00	74.50	72.50	71.25
Min, Max	25.3, 183.3	15.5, 208.8	24.3, 205.3	8.8, 179.5	8.8, 205.3	8.8, 208.8

Abbreviations: BMI, body mass index; ER, extended release; LPS, latency to persistence sleep; SD, standard deviation; SE, sleep efficiency; TST, total sleep time; WASO, wake after sleep onset; WASO2H, minutes of wake in the 2nd half of polysomnography recording.
Notes: Baseline sleep diary variables are the mean of diary data entered on the last 7 mornings before the first Baseline Polysomnography during the Run-In Period.
Source: Adapted from Applicant's Clinical Study Report E2006-G000-304, Table 14.1.4.1.1.2, Listing 16.2.6.5.1

Clinical Reviewer Comments*: Weight, height, BMI, and baseline sleep parameters appear to be balanced across the groups. The baseline sleep parameters seem balanced across the groups.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance: As assessed by pill counts, the majority of subjects (>95%) were ≥80% to ≤100% compliant with study drug during the Run-in Period. During the Treatment Period, the majority of subjects (>95%) were ≥80% to ≤100% compliant with lemborexant and zolpidem. Overall, during the Treatment Period, 13 subjects were >120% compliant with lemborexant and zolpidem. In each of these cases, it was determined that the high compliance rate was an artifact of how treatment compliance was calculated rather than overdose or abuse of the study drug. Overall, the compliance rates by pill counts is considered acceptable but pill counts may overestimate or underestimate compliance.

Rescue Medication: The study protocol prohibited the use of other treatments for insomnia during the study. aberrant use of other medications is reviewed in Section 8.1.2.5, *Protocol Violations/Deviations.*

Concomitant Medication: The Applicant reports that a similar number of subjects in each group took concomitant medications at baseline, ranging from 71.3% to 77.1% of subjects. During the treatment period, the range was 72.0% to 81.2%. The most commonly reported concomitant medication during the treatment period in the LEM10, LEM5, ZOL, and PBO treatment groups were vitamins (15.3%, 15.0%, 17.9%, and 19.6% of subjects, respectively).

Clinical Reviewer Comments*: Concomitant medication use can cause confounding results, but the study was not designed to determine their influence on efficacy (e.g., the timing, dosages, duration, and reason for the concomitant medication was not described). However, the rates of concomitant medication use are reasonably balanced across groups and is not expected to impact the interpretation of study results.*

8.1.2.7. Efficacy Results – Primary Endpoint

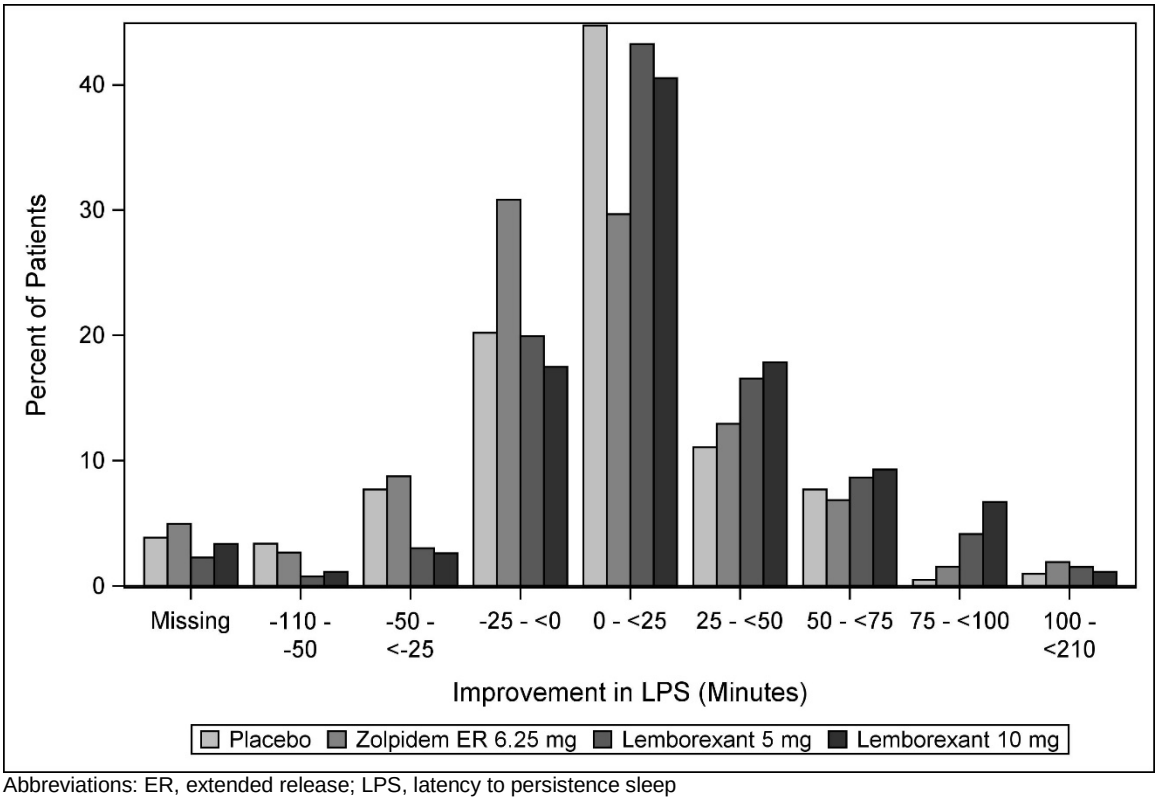
A summary of statistical significance for the primary efficacy endpoints according to the hierarchical testing procedure is provided in Table 50. The results on the primary efficacy endpoint were statistically significant for lemborexant 5 mg and 10 mg. No sensitivity analysis was performed because of the negligible amount (<5%) of missing data. Figure 31 displays the histogram of the magnitude of improvement from baseline in LPS at Days 29/30. To explore the distribution of LPS, histograms of LPS and log(LPS) with normal density are presented in Figure 32 and Figure 33. Based on the plots, the assumption of log normal distribution of LPS seems reasonable.

Table 50: Primary Efficacy Results on LPS (Minutes), Study E2006-G000-304

Treatment Group	# ITT subject	Baseline Geomean Score (SD)	Day 29/30 LSGM (SE)	LSGM Ratio: Day 29/30/Baseline (95% CI)	LSGM Treatment Ratio: Active/Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	208	33.6 (25.9)	20.0 (1.1)	0.70 (0.62, 0.78)		
Zolpidem ER 6.25 mg	263	31.0 (28.5)	24.4 (1.3)	0.85 (0.77, 0.94)	1.22 (1.06, 1.40) 0.006	
Lemborexant 5 mg	266	33.0 (27.2)	15.5 (0.8)	0.54 (0.49, 0.60)	0.77 (0.67, 0.89) <0.001	Yes
Lemborexant 10 mg	269	33.3 (27.2)	14.5 (0.7)	0.51 (0.46, 0.56)	0.72 (0.63, 0.83) <0.001	Yes

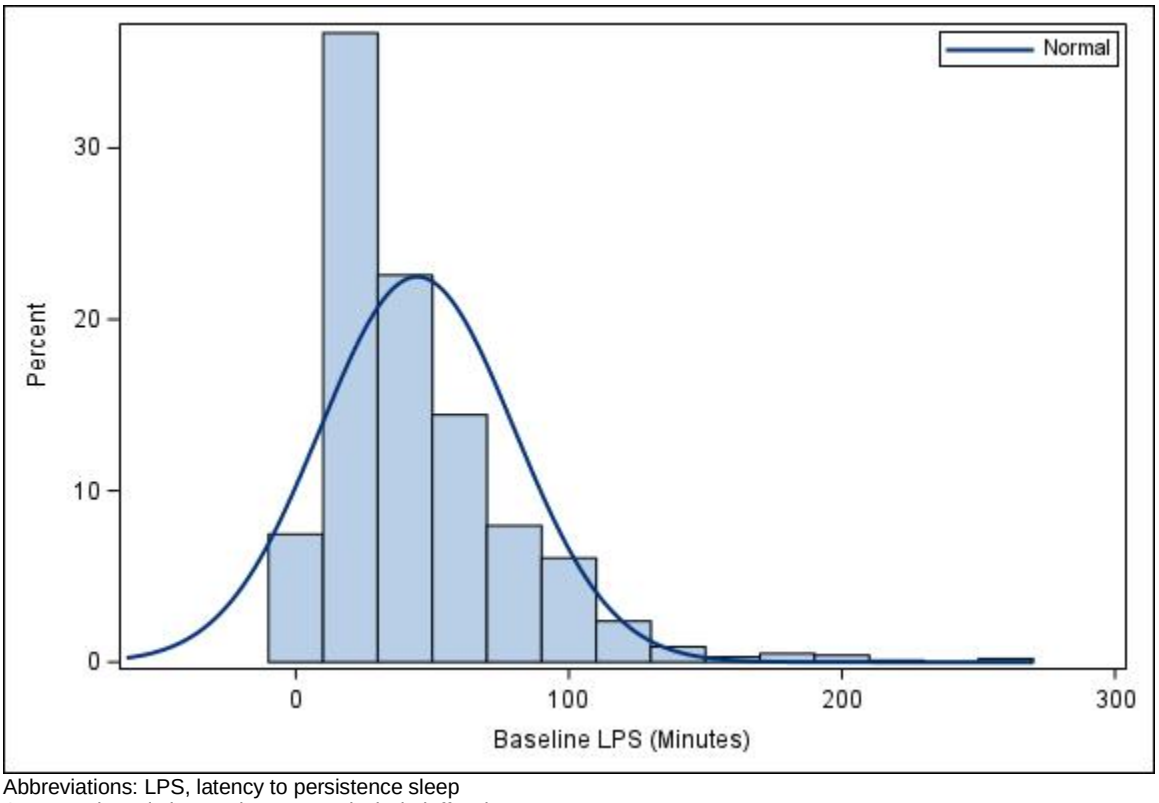
Abbreviations: CI, confidence interval; ER, extended release; ITT, intention to treat; LPS, latency to persistence sleep; LSGM, least squares geometric mean; MCP, multiple comparison procedures; p-value, probability value; SD, standard deviation; SE, standard error
Note: CI were not adjusted with multiplicity
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 31: Histogram of the Magnitude of Improvement from Baseline in LPS at Days 29/30, E2006-G000-304



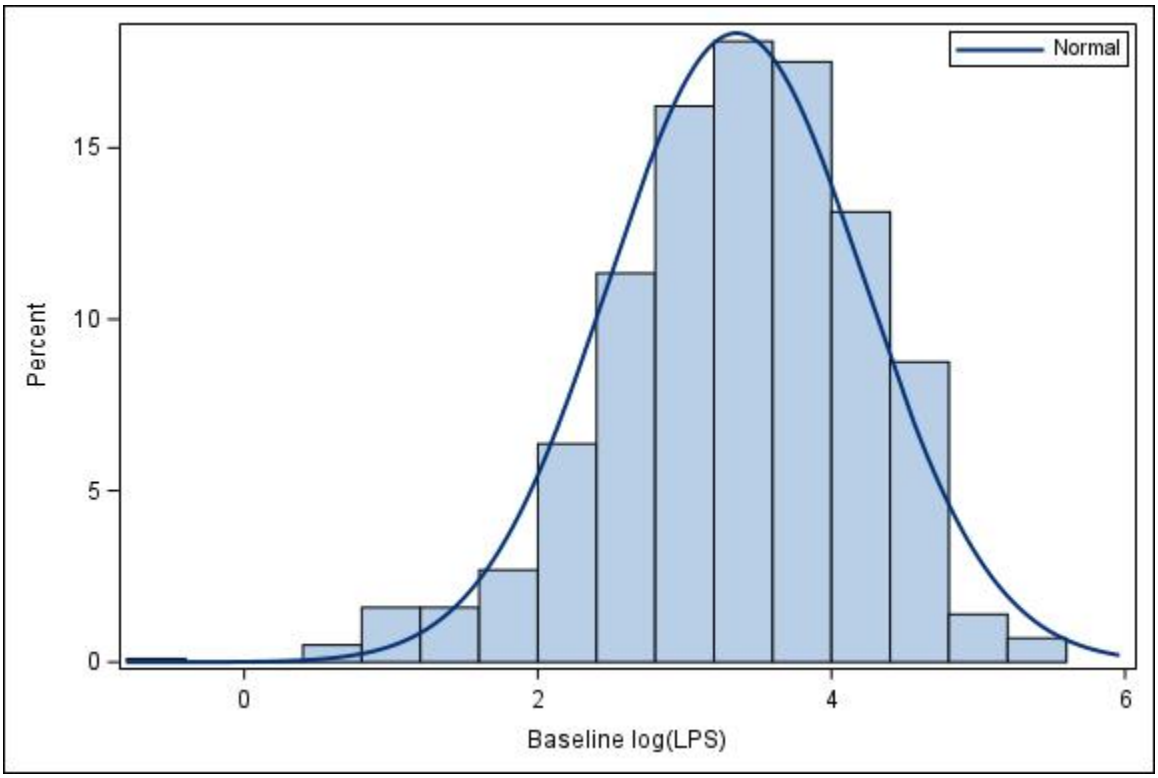
Abbreviations: ER, extended release; LPS, latency to persistence sleep
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 32: Histogram of Non-Missing Baseline LPS, Study E2006-G000- 304



Abbreviations: LPS, latency to persistence sleep
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

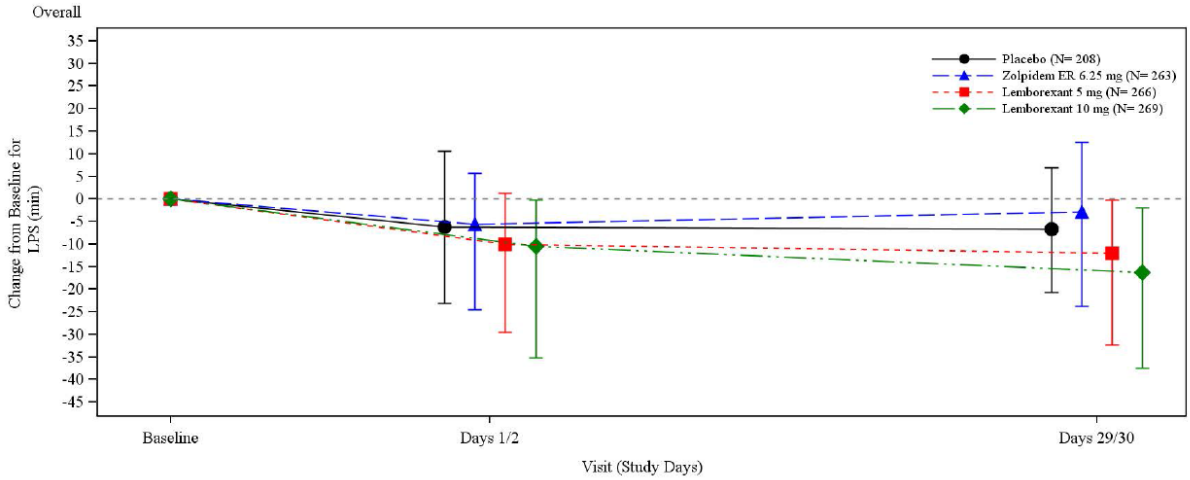
Figure 33: Histogram of Non-Missing Baseline log(LPS), Study E2006-G000-304



Abbreviations: LPS, latency to persistence sleep
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

The observed time course of LPS during the 1-month double blind period is graphically presented in Figure 34. All treatment groups showed a decrease in LPS score over 1 month, with numerically greater change from baseline for both lemborexant groups at Day 1/2 and Days 29/30. The zolpidem group has numerically worse results than the placebo group at Days 29/30.

Figure 34: Medians (1st and 3rd Quartiles) for Change from Baseline for LPS, Study E2006-G000-304

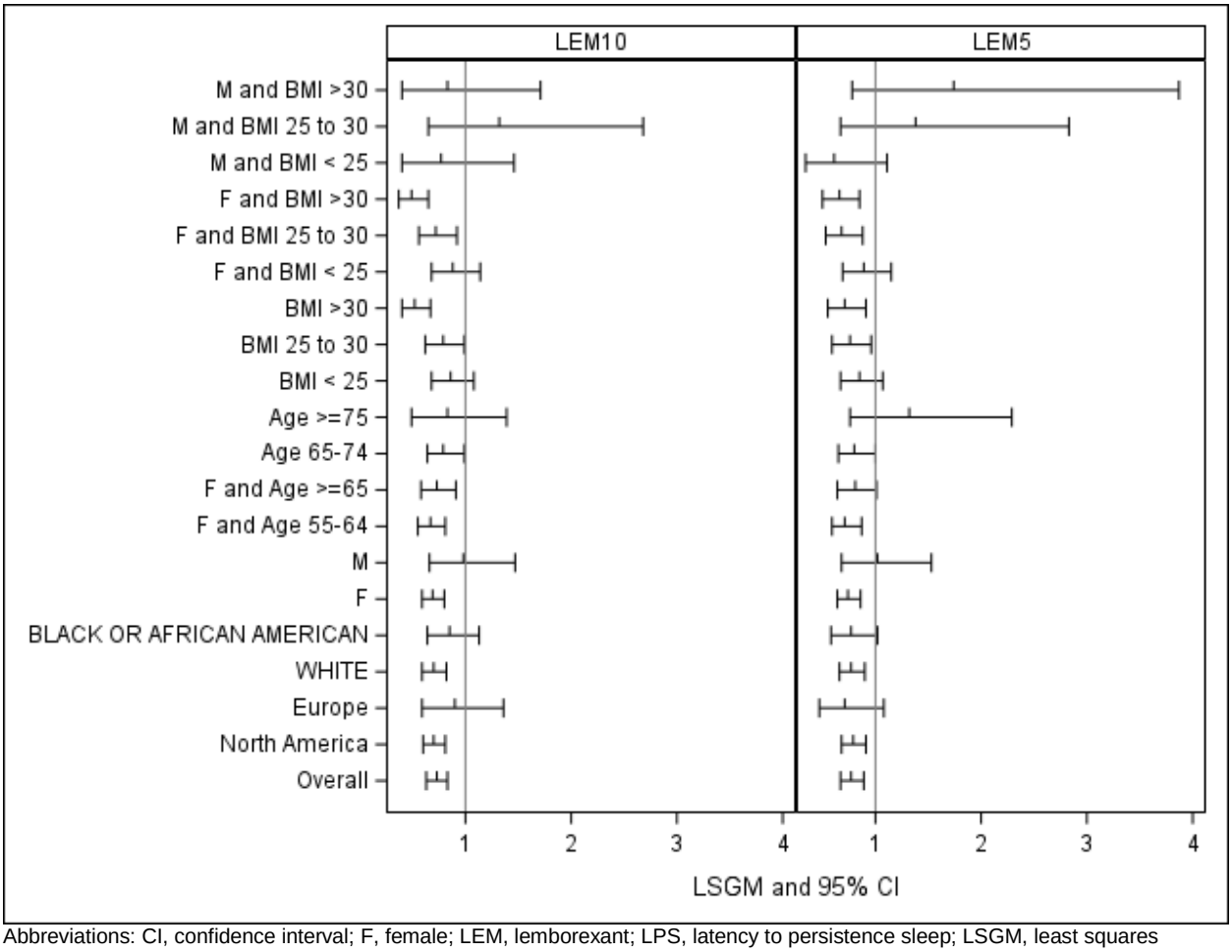


Abbreviations: ER, extended release; LPS, latency to persistence sleep
Source: Sponsor's Figure 3 in CSR, Study E2006-G000-304

***Clinical Reviewer Comments**: The primary efficacy results suggest that zolpidem appeared to perform worse than placebo on the primary efficacy endpoint. This is inconsistent with clinical expectations and results from clinical trials testing zolpidem. Notably, the drug development program for zolpidem ER (Ambien CR) specified the primary endpoint at 2 weeks, compared to 29/30 days in this study. Per the AMBIEN CR label, "AMBIEN CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment." Furthermore, Study 304 was conducted in older females and elderly males. Therefore it is possible that the efficacy of zolpidem is not consistent beyond 2 weeks, particularly in elderly subjects.*

Further exploratory subgroup analyses on the primary endpoint were assessed by age group, race, gender, baseline BMI, and interaction between gender and baseline BMI. Results are shown in Figure 35. There are a few small size subgroups with effect favoring placebo. The estimates in the smaller subgroups are subject to large sampling variation. To further investigate the subgroup effect, the FDA reviewer performed subgroup analyses on two key secondary endpoints, SE and WASO. The results are shown in Figure 37 and Figure 39. For SE and WASO, all the subgroups have effect favoring lemborexant. This further supports that the observed deviation of the subgroup effect in LPS may be caused by sample variation and not subgroup differences. However, subgroups are small and most were not powered for subgroup analyses, thus limiting interpretation of these findings.

Figure 35: LSGM Treatment Ratio (Active/Placebo) with 95% CI in LPS by Subgroup, Study E2006-G000-304



Abbreviations: CI, confidence interval; F, female; LEM, lemborexant; LPS, latency to persistence sleep; LSGM, least squares geometric mean; M, male; MMRM, mixed effect model repeated measurement
Source: Biostatistics Reviewer's Analysis (adeff.xpt)
Based on MMRM Analysis

Data Quality and Integrity

The Applicant reports the study was organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

8.1.2.8. Efficacy Results – Key Secondary Endpoints

A summary of statistical significance for the pre-specified key secondary efficacy endpoints according to the hierarchical testing procedure is provided in Table 51, Table 52, and Table 53. The results on all three key secondary efficacy endpoints were considered statistically significant for lemborexant 5 mg and 10 mg. No sensitivity analysis was performed because of the negligible amount (<5%) of missing data. Figure 36, Figure 38, and Figure 40 display the histograms of the magnitude of improvement from baseline in SE, WASO, and WASO2H at Days 29/30, respectively. Although the comparisons of lemborexant to Zolpidem in WASO2H were

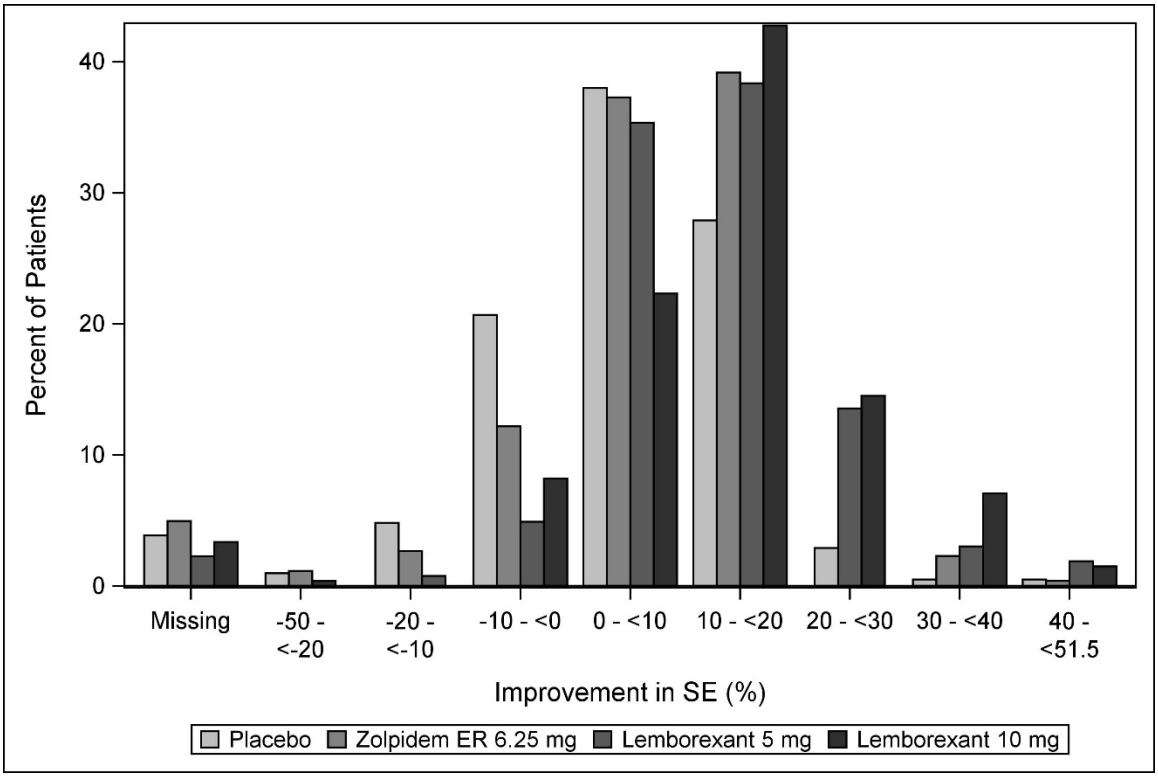
statistically significant, Zolpidem was statistically worse than placebo in the primary endpoint, LPS. Therefore, the comparison of lemborexant to Zolpidem is not informative to be included in the labeling.

Table 51: Efficacy Results on Key Secondary Endpoint SE (%), Study E2006-G000-304

Treatment Group	# ITT subject	Baseline Mean (SD)	Day 29/30 LS mean (SE)	LS Mean Change from Baseline (95% CI)	LS Mean Treatment Difference: Active-Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	208	68.9 (9.6)	74.6 (0.6)	6.3 (0.6)		
Zolpidem ER 6.25 mg	263	68.1 (11.4)	76.7 (0.5)	9.5 (0.5)	3.2(1.7, 4.6) p=<.001	
Lemborexant 5 mg	266	68.4 (11.3)	80.7 (0.5)	13.4 (0.5)	7.1(5.6, 8.5) p=<.001	Yes
Lemborexant 10 mg	269	67.8 (10.8)	82.7 (0.5)	14.4 (0.5)	8.0(6.6, 9.5) p=<.001	Yes

Abbreviations: ER, extended release; CI, confidence interval; ITT, intention to treat; LS, least squares; MCP, multiple comparison procedures; p-value, probability value; SD, standard deviation; SE, sleep efficiency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

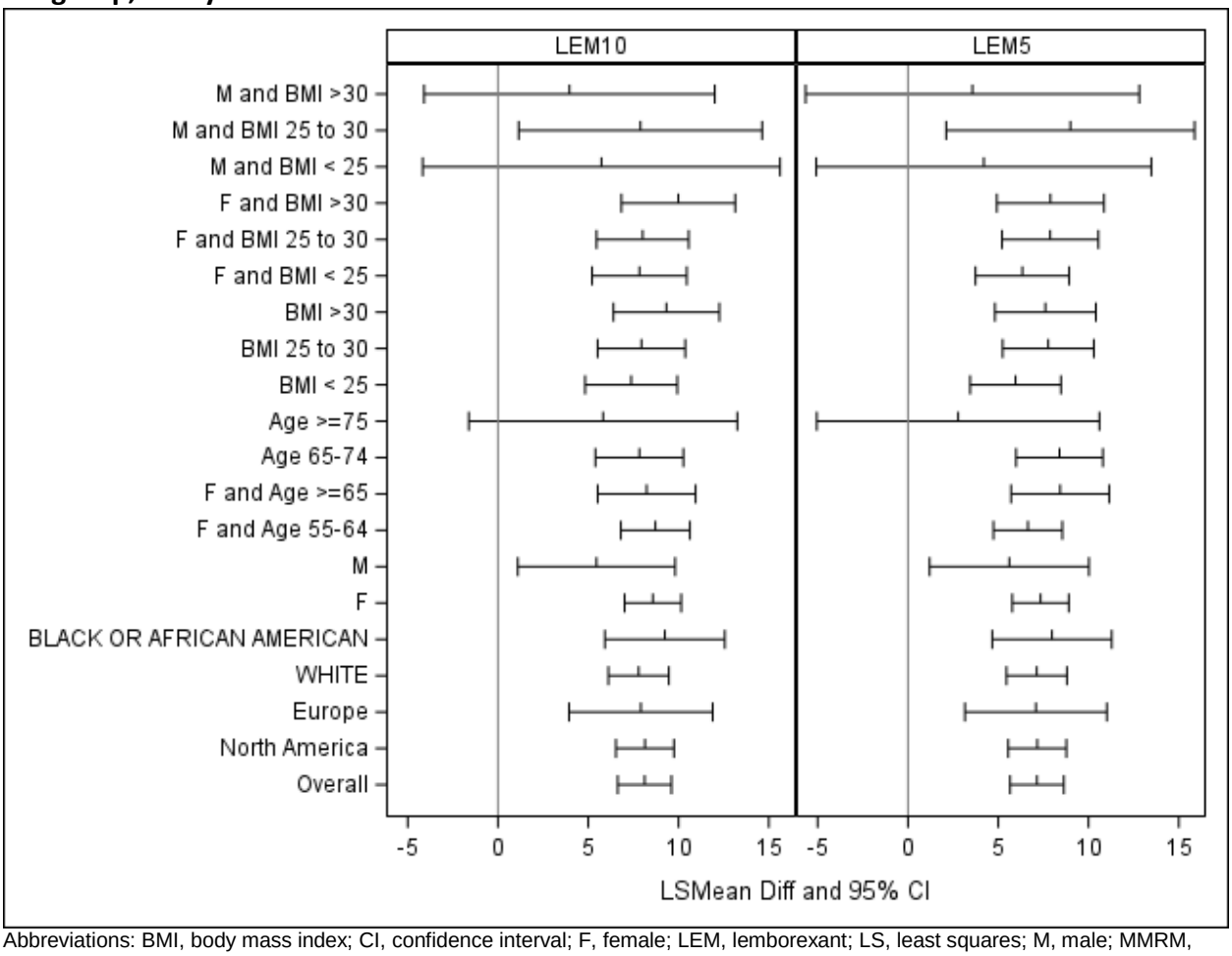
Figure 36: Histogram of the Magnitude of Improvement from Baseline in SE at Days 29/30, Study E2006-G000-304



Abbreviations: ER, extended release; SE, sleep efficiency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Clinical Reviewer Comments*: The secondary efficacy tables and histograms provide some additional clinically meaningful information regarding the efficacy findings of lemborexant. For example, early morning awakening is a possible component of insomnia, so the significant results on the key secondary endpoint (e.g., histogram bins for 30-<60 and 60-<90) provide evidence of benefit on an aspect of insomnia that isn't assessed by the primary efficacy measure (or as directly by the WASO or SE).*

Figure 37: Least Squares Mean Treatment Difference (Active – Placebo) With 95% CI in SE by Subgroup, Study E2006-G000-304



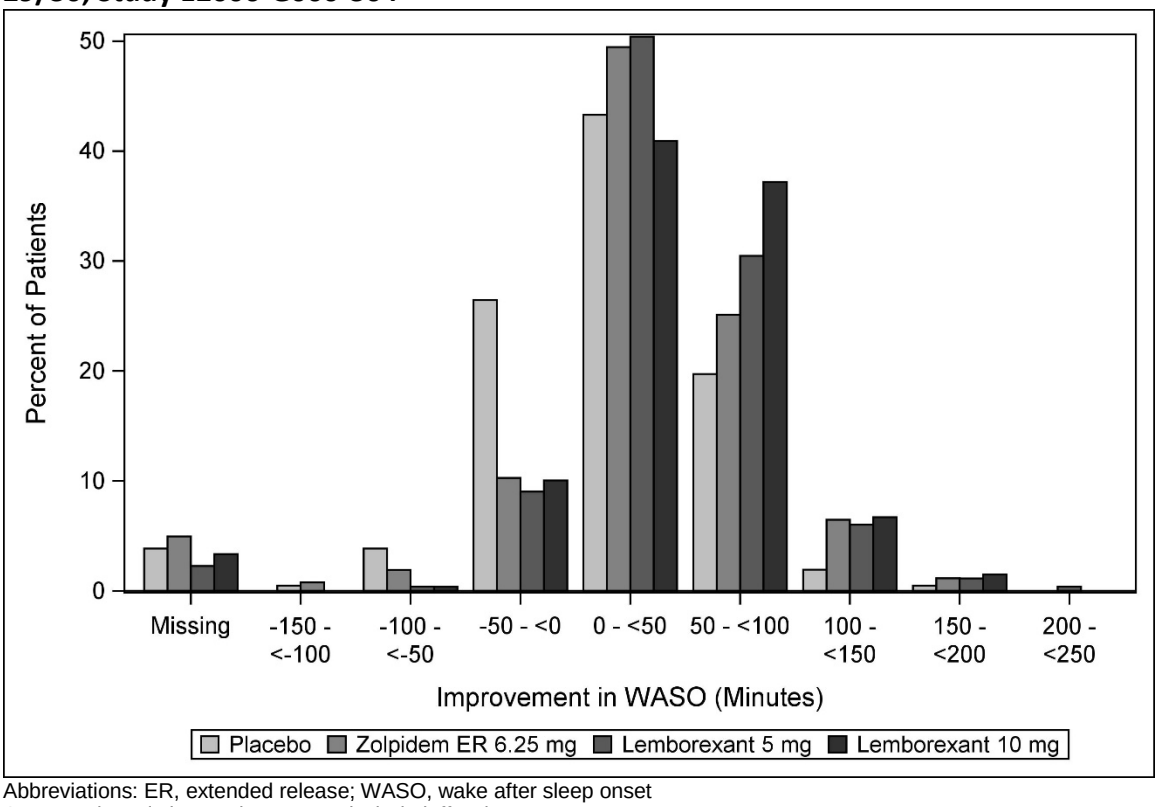
Abbreviations: BMI, body mass index; CI, confidence interval; F, female; LEM, lemborexant; LS, least squares; M, male; MMRM, mixed effect model repeated measurement; SE, sleep efficiency
Source: Biostatistics Reviewer's Analysis (adeff.xpt)
Based on MMRM Analysis

Table 52: Efficacy Results on Key Secondary Endpoint WASO (Minutes), Study E2006-G000-304

Treatment Group	# ITT subject	Baseline Mean (SD)	Day 29/30 LS Mean (SE)	LS Mean Change from Baseline (95% CI)	LS Mean Treatment Difference: Active-Placebo (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	208	111.7 (37.2)	92.2 (2.5)	-21.4 (2.5)		
Zolpidem ER 6.25 mg	263	114.3 (39.9)	76.0 (2.2)	-37.7 (2.2)	-16.2 (-22.3, -10.2) p=<.001	
Lemborexant 5 mg	266	113.4 (39.0)	68.3 (2.2)	-45.4 (2.2)	-24.0 (-30.0, -18.0) p=<.001	Yes
Lemborexant 10 mg	269	114.8 (40.0)	66.9 (2.2)	-46.8 (2.2)	-25.3 (-31.4, -19.3) p=<.001	Yes

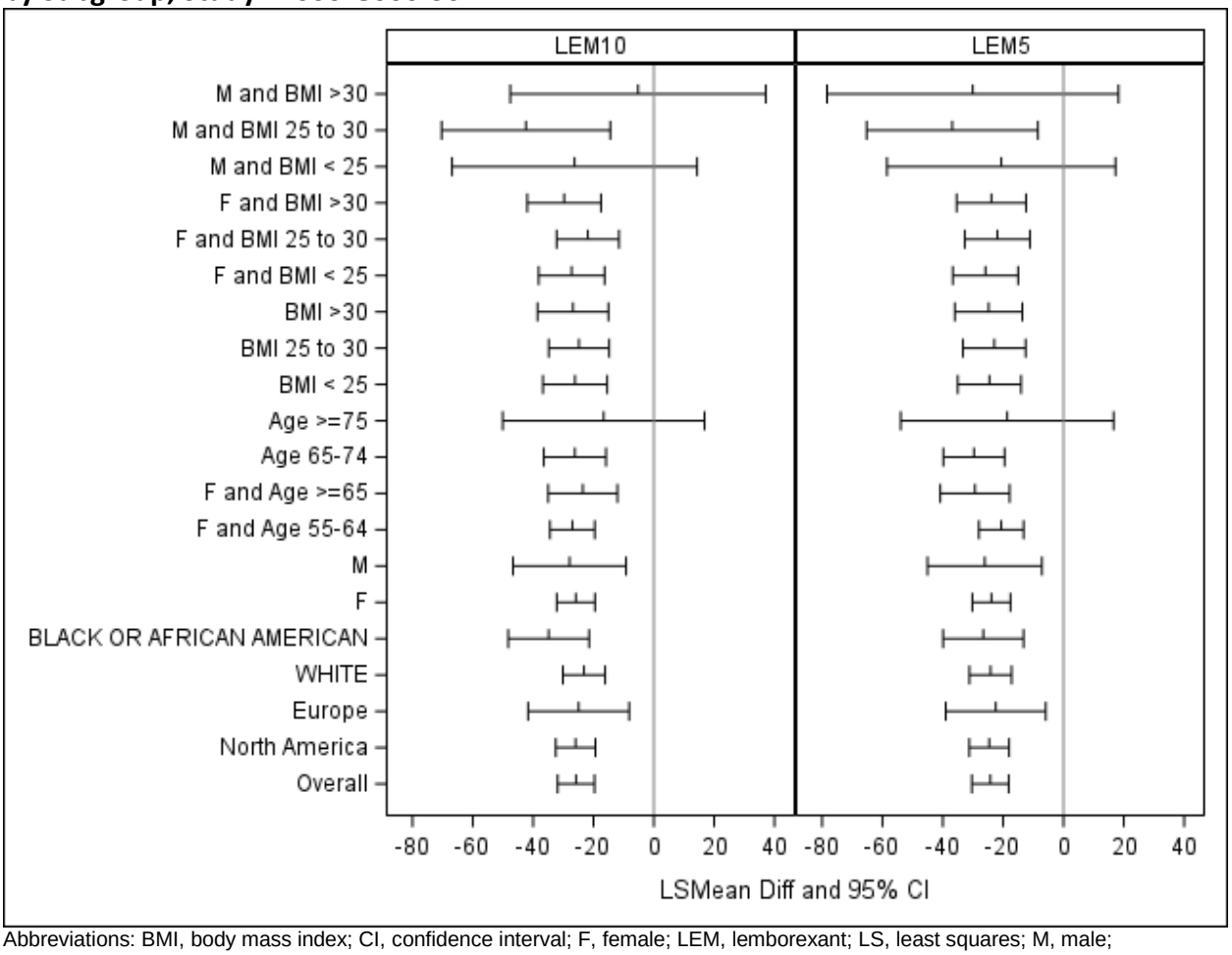
Abbreviations: CI, confidence interval; ER, extended release; ITT, intention to treat; LS, least squares; MCP, multiple comparison procedures; p-value, probability value; SD, standard deviation; WASO, wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 38: Histogram of the Magnitude of Improvement From Baseline in WASO at Days 29/30, Study E2006-G000-304



Abbreviations: ER, extended release; WASO, wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 39: Least Squares Mean Treatment Difference (Active – Placebo) With 95% CI in WASO by Subgroup, Study E2006-G000-304



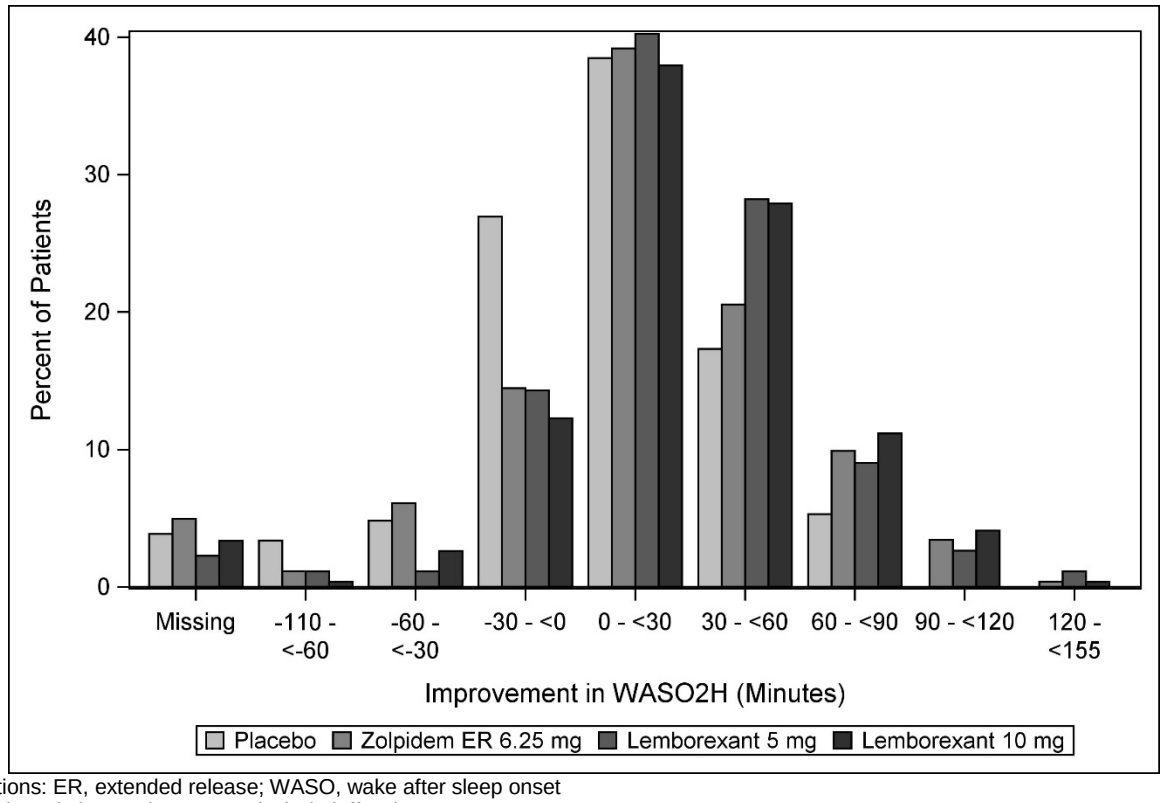
Abbreviations: BMI, body mass index; CI, confidence interval; F, female; LEM, lemborexant; LS, least squares; M, male; MMRM, mixed effect model repeated measurement; WASO, wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)
Based on MMRM analysis

Table 53: Efficacy Results on Key Secondary Endpoint WASO2H (Minutes), Study E2006-G000-304

Treatment Group	# ITT subject	Baseline Mean (SD)	Day 29/30 LS Mean (SE)	LS Mean Change from Baseline (95% CI)	LS Mean Treatment Difference: Active-Zolpidem (95% CI) Unadjusted p-value	Significance (MCP-adjusted)
Placebo	208	74.4 (30.1)	65.6 (2.0)	-11.0 (2.0)		
Zolpidem ER 6.25 mg	263	78.0 (33.8)	55.9 (1.8)	-20.7 (1.8)		
Lemborexant 5 mg	266	76.6 (32.9)	49.2 (1.7)	-27.4 (1.7)	-6.6(-11.2, -2.1) p=0.004	Yes
Lemborexant 10 mg	269	76.9 (32.1)	47.9 (1.8)	-28.7 (1.8)	-8.0(-12.5, -3.5) p=<.001	Yes

Abbreviations: CI, confidence interval; ER, extended release; ITT, intention to treat; LS, least squares; MCP, multiple comparison procedures; p-value, probability value; SD, standard deviation; WASO, wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Figure 40: Histograms of the Magnitude of Improvement From Baseline in WASO2H, Study E2006-G000-304



Abbreviations: ER, extended release; WASO, wake after sleep onset
Source: Biostatistics Reviewer's Analysis (adeff.xpt)

Dose/Dose Response

Review of the above results demonstrates an inconsistent pattern of increase in efficacy from LEM5 to LEM10. A greater percent of patients reached defined levels of improvement on the histograms with LEM10 than LEM5 (for example, Figure 39 – magnitude of improvement in WASO 50-<100 minutes), so it is possible that certain patients may experience greater benefit with LEM10 than LEM5. This may be in part due to the dose response curve described in Section 6.3.2.1 and Section 8.1.2, which demonstrates minimal change in SE from LEM5 to LEM10.

Durability of Response

The effect of the drug over time was measured by the primary endpoint of change from baseline to end of treatment at 1 month as noted in the above efficacy results. The study drug appears to maintain effectiveness over this time for insomnia disorder. However, there were no intermediate primary endpoints, so the course of efficacy could not be mapped.

Persistence of Effect

Persistence of Effect was not assessed as part of Study 304.

Efficacy at the Beginning of Treatment

The primary efficacy endpoint in Study 304 was the mean change in LPS from baseline to Days 29 and 30. The Applicant also specified the mean change in LPS from baseline to Days 1 and 2 as a secondary endpoint, without pre-specifying statistical tests for this endpoint which control for type I error. At both the beginning of treatment (Days 1/2) and at the end of treatment (Days 29/30), the change from baseline in LPS was greater in subjects receiving LEM5 or LEM10 than in those receiving placebo (see Table 54**)**.

Table 54: Secondary Endpoints, PSG Assessments of Sleep Parameters in Study 304

	PBO (N=208)	LEM5 (N=266)	LEM10 (N=269)	Difference between LEM and Placebo	
				LEM5	LEM10
Sleep Maintenance (SE), %					
Baseline (mean)	69	68	68		
Days 1/2 LSM Change from Baseline	5	14	17	9*	12*
Days 29/30 LSM Change from Baseline	6	13	14	7*	8*
Sleep Maintenance (WASO), minutes					
Baseline (mean)	112	113	115		
Days 1/2 LSM Change from Baseline	-18	-51	-60	-33*	-42*
Days 29/30 LSM Change from Baseline	-21	-45	-47	-24*	-25*
Sleep Maintenance (WASO2H), minutes					
Baseline (mean)	74	77	77		
Days 29/30 LSM Change from Baseline	-9	-30	-37	-22*	-28*
Days 29/30 LSM Change from Baseline	-11	-27	-29	-16*	-18*

Abbreviations: ER, extended release; LEM, lemborexant; LPS, latency to persistent sleep; LSGM, least squares geometric mean;
LSM, least squares mean; PBO, placebo; PSG, polysomnography; SE, sleep efficiency; WASO, wake after sleep onset; ZOL, zolpidem. *p>0.05
Source: Applicant Table 2.5-2

Clinical Reviewer Comments*: For Study 304, the effect of lemborexant on secondary endpoints at Days 1/2 were generally consistent with the later timepoint (primary efficacy endpoint) of Days 29/30. Although the change from baseline to Days 1/2 was not a pre-specified endpoint within the statistical hierarchy, this information is considered highly relevant to clinicians and warrants inclusion in labeling with careful language that does not suggest that this was a pre-specified endpoint with appropriate type I error control. Please see Section 11 for additional discussion.*

8.1.3. Integrated Review of Effectiveness

8.1.3.1. Assessment of Efficacy Across Trials

The efficacy of lemborexant for the treatment of insomnia has been evaluated in two multicenter, randomized, placebo-controlled studies conducted in subjects with insomnia disorder. Table 55 summarizes the Applicant's efficacy parameters evaluated in Studies 303 and 304.

Table 55: Efficacy Parameters Evaluated in the Phase 3 Program by Dose

Efficacy Parameters			Study 303		Study 304	
			LEM5	LEM10	LEM5	LEM10
Nocturnal Assessments	Sleep Onset	Latency to Persistent Sleep (LPS) (Primary Endpoint, 304)	-	-	X	X
		Subjective Sleep Onset Latency (sSOL) (Primary Endpoint, 303)	X	X	X	X
	Sleep Maintenance	Sleep Efficiency (SE) (Secondary Endpoint, 304)	-	-	X	X
		Subjective Sleep Efficiency (sSE) (Secondary Endpoint, 303)	X	X	X	X
		Wake After Sleep Onset (WASO) (Secondary Endpoint, 304)	-	-	X	X
		Subjective Wake After Sleep Onset (sWASO) (Secondary Endpoint, 303)	X	X	X	X
	Sleep Maintenance in the Second Half of the Night	Wake After Sleep Onset in the Second Half of the Night (WASO2H) (Secondary Endpoint, 304)	-	-	X	X
Daily Functioning	Impact of Insomnia	ISI (Exploratory Endpoint)	X	X	X	X
	Fatigue	FSS (Exploratory Endpoint)	X	X	X	X

Efficacy Parameters			Study 303		Study 304	
			LEM5	LEM10	LEM5	LEM10
Patient-Reported Impression of Efficacy	Subjects' perception of the effect of study drug	PGI-I (Exploratory Endpoint)	X	X	X	X

Abbreviations: FSS, Fatigue Severity Scale; ISI, Insomnia Severity Index; LEM, lemborexant; LPS, latency to persistent sleep; PGI-I, Patient Global Impression – Insomnia; SE, sleep efficiency; sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; WASO2H, wake after sleep onset in the second half of the night; sWASO, subjective wake after sleep onset; WASO, wake after sleep onset
Source: Applicant's ISE, Table 4

8.1.3.1.1. Primary Endpoints

The Applicant's prespecified primary endpoints demonstrated statistical significance in both phase 3 efficacy trials. The primary efficacy endpoint in Study 303 was the mean change from Study Baseline in log(sSOL) at month 6. The primary endpoint in Study 304 was change from baseline to end of study in log(LPS). Both sSOL and LPS are measured in minutes, with a decrease in value indicating improvement in terms of taking less time to fall asleep. Table 56 demonstrates the effectiveness of the prespecified primary endpoint results for both studies 303 and 304.

Table 56: Results for the Primary Endpoint (Studies 303 and 304)

Study Number	Primary Efficacy Endpoint	Treatment Group (# ITT subject)	Baseline GM (SD)	GM (SD)	LSGM Ratio vs Baseline (95% CI)	Placebo-divided LSGM Ratio (95% CI)
303	CFB in sSOL at Month 6	Placebo (n=318)	45.0 (31.8)	27.4 (27.5)	0.62(0.56, 0.68)	
		LEM 5 (n=316)*	43.0 (31.5)	18.6 (16.4)	0.45(0.41, 0.50)	0.73 (0.64, 0.84)
		LEM 10 (n=315)*	45.0 (33.4)	19.4 (19.1)	0.43(0.39, 0.48)	0.70 (0.61, 0.81)
304	CFB in LPS on Days 29/30	Placebo (n=208)	33.6 (25.9)	24.9 (23.1)	0.70 (0.62, 0.78)	
		LEM 5 (n=266)*	33.0 (27.2)	18.9 (15.8)	0.54 (0.49, 0.60)	0.77 (0.67, 0.89)
		LEM10 (n=269)*	33.3 (27.2)	17.5 (13.6)	0.51 (0.46, 0.56)	0.72 (0.63, 0.83)

Abbreviations: CFB, change from baseline; CI, confidence interval; GM, geometric mean; ITT, intention to treat; LEM, lemborexant; LPS, latency to persistent sleep; LS, least squares; LSGM, least squares geometric mean; SD, standard deviation; sSOL, subjective sleep onset latency
* statistically significant after multiplicity adjustment
Source: Modified from Biostatistic Reviewer's Analysis (adeff.xpt)

8.1.3.1.2. Secondary and Other Endpoints

Results from the primary efficacy endpoints demonstrated the improvement in sleep onset of LEM5 and LEM10 compared to placebo. The secondary endpoints were the only endpoints to examine sleep maintenance. Clinically meaningful improvements were reported for LEM5 and/or LEM10 compared to placebo, including improvements in change from baseline to end of treatment sSE and sWASO in Study 303 and SE%, WASO, and WASO2H in Study 304.

Study 303 demonstrated durability of response over time, for example sSOL continued to demonstrate clinically meaningful results at 1, 2, 3, 4, 5 and 6 months.

8.1.3.1.3. Subpopulations

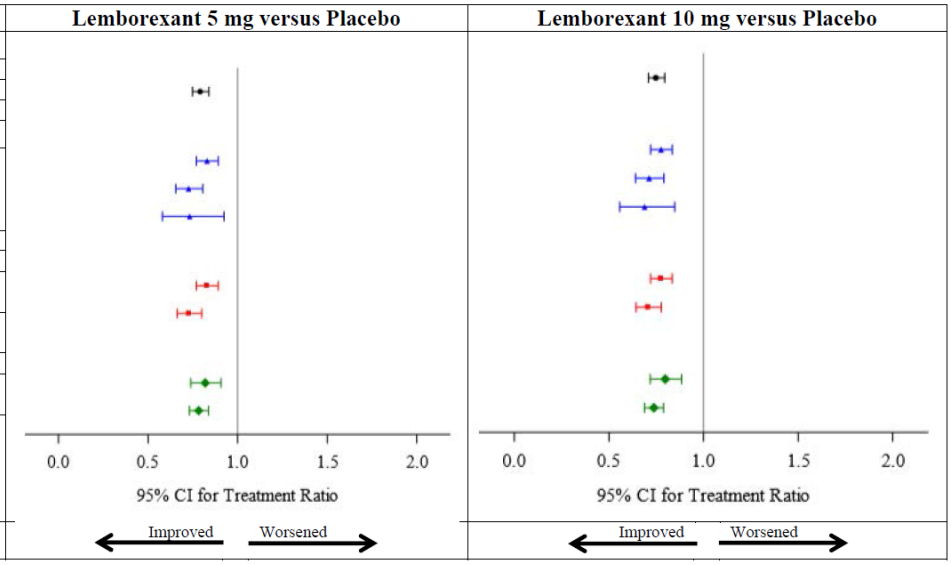
The Applicant presented summary efficacy results for several subpopulations, including Age, Sex, Race, and BMI. Efficacy was described for each subgroup during the First 7 days and at Month 1 of treatment.

Figure 41 to Figure 46 display Forest plots for sSOL, sSE, sWASO by subgroup using pooled data from studies 303 and 304. The randomization ratios for studies 303 and 304 were considered similar enough to permit pooling. The lengths of the study were not equal; however, the outcomes tested below are all change from baseline to either 7 days or 30 days, thus allowing for exploratory pooling of the two studies. Notably, in Study 304, the primary efficacy measure was collected by PSG, but the Applicant also collected sSOL from diaries as a secondary endpoint (which are grouped with the sSOL data from study 303).

Sex and Age: In phase 3 studies, the subpopulation analyses suggest an overall trend for the efficacy of for LEM5 and LEM10 versus placebo by age and sex for sSOL at 7 days (Figure 41) and 1 month (Figure 42) of treatment, for sSE (Figures 43 and 44) and for sWASO (Figures 45 and 46). Some subgroups have error bars that cross 1; however, the subgroups were often small (i.e., age ≥75), so the confidence intervals were wide in some cases.

Figure 41: Forest Plot of Change from Baseline for First 7 Days – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sSOL

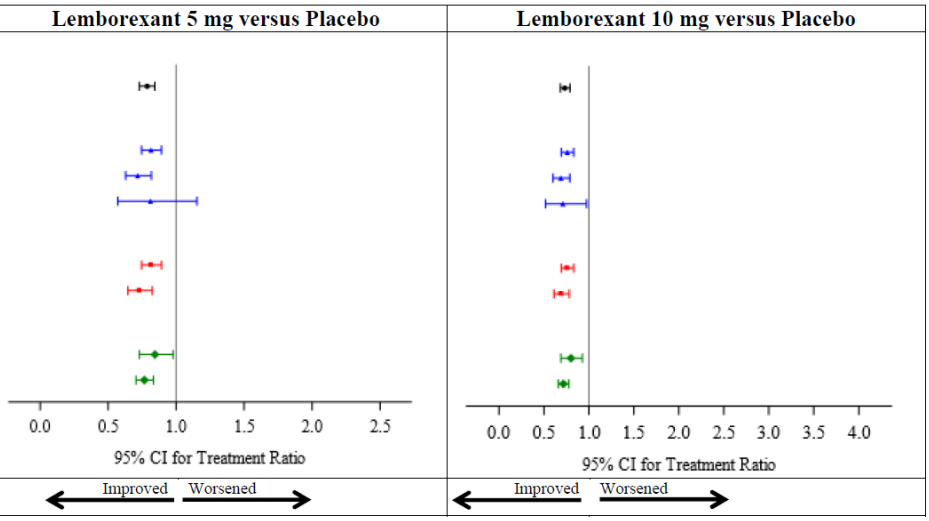
Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	517	569	576
Age group 1 (years)			
	N	N	N
<65	340	368	371
≥65-<75	148	175	160
≥75	29	26	45
Age group 2 (years)			
	N	N	N
<65	340	368	371
≥65	177	201	205
Sex			
	N	N	N
Male	122	141	132
Female	395	428	444



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sSOL, subjective sleep onset latency
Source: Applicant ISE Figure 12

Figure 42: Forest Plot of Change from Baseline for One Month – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sSOL

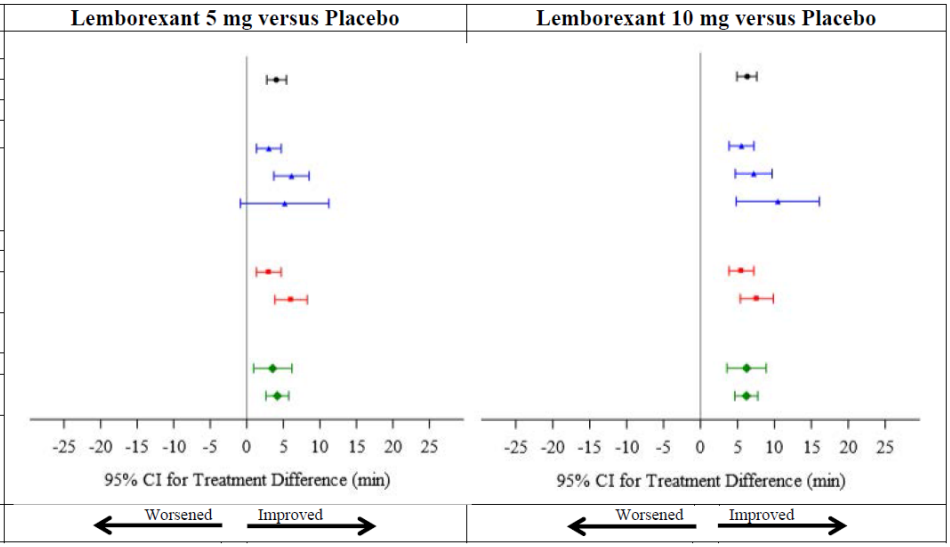
Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	495	550	555
Age group 1 (years)			
	N	N	N
<65	320	355	358
≥65-<75	147	170	156
≥75	28	25	41
Age group 2 (years)			
	N	N	N
<65	320	355	358
≥65	175	195	197
Sex			
	N	N	N
Male	117	138	126
Female	378	412	429



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sSOL, subjective sleep onset latency
Source: Applicant ISE Figure 13

Figure 43: Forest Plot of Change from Baseline for First 7 Days – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sSE

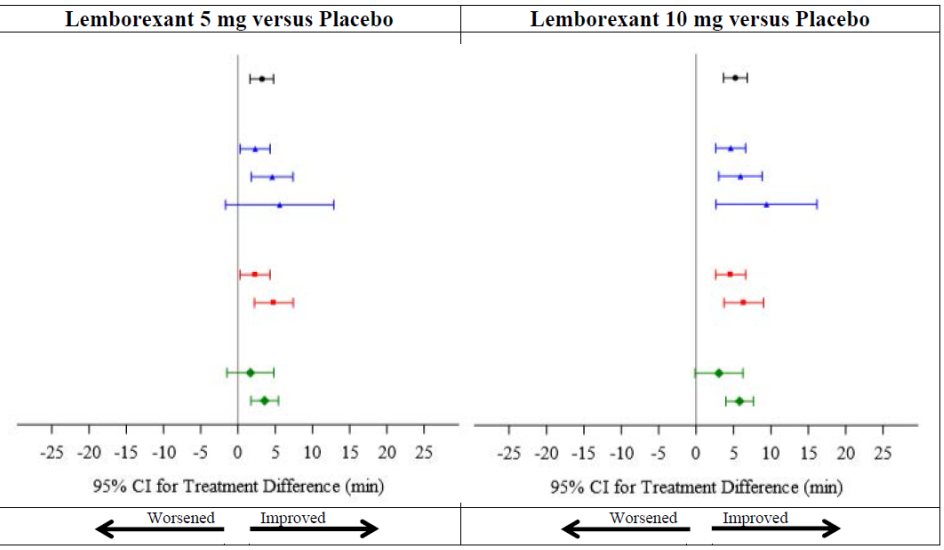
Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	501	546	550
Age group 1 (years)			
	N	N	N
<65	330	352	361
≥65-<75	143	169	149
≥75	28	25	40
Age group 2 (years)			
	N	N	N
<65	330	352	361
≥65	171	194	189
Sex			
	N	N	N
Male	117	133	126
Female	384	413	424



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sSE, subjective sleep efficiency
Source: Applicant ISE Figure 16

Figure 44: Forest Plot of Change from Baseline for One Month – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sSE

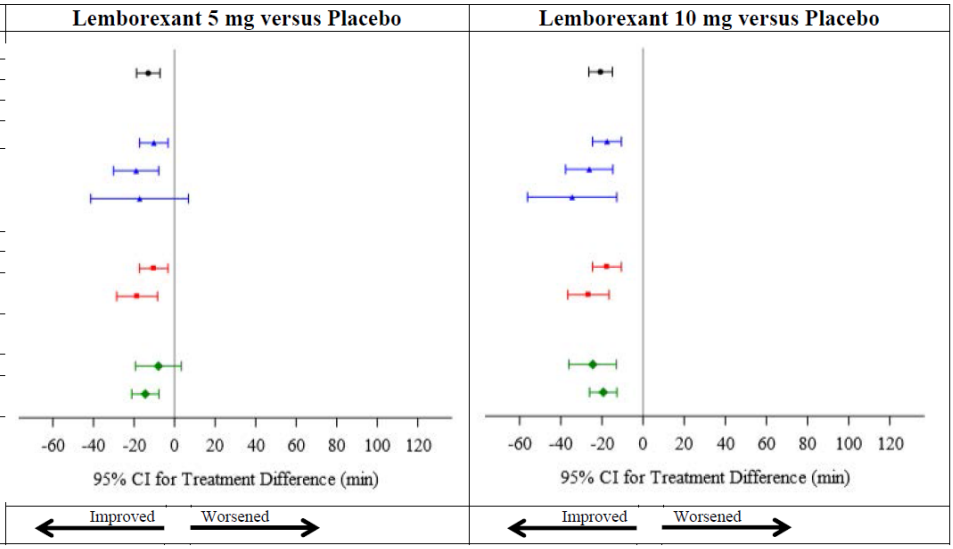
Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	481	529	526
Age group 1 (years)			
	N	N	N
<65	313	342	346
≥65-<75	141	162	144
≥75	27	25	36
Age group 2 (years)			
	N	N	N
<65	313	342	346
≥65	168	187	180
Sex			
	N	N	N
Male	113	131	119
Female	368	398	407



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sSE, subjective sleep efficiency
Source: Applicant ISE Figure 17

Figure 45: Forest Plot of Change from Baseline for First 7 Days – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sWASO

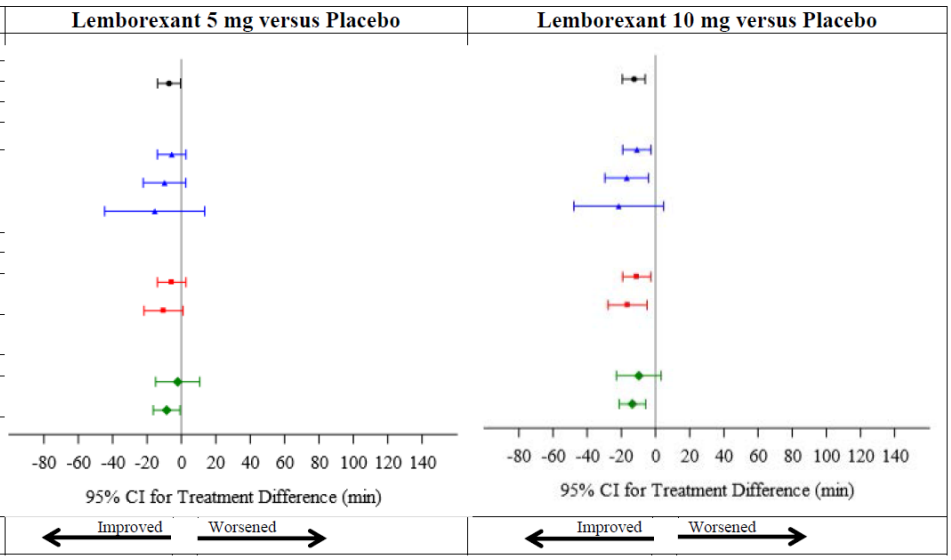
Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	515	569	571
Age group 1 (years)			
	N	N	N
<65	339	369	369
≥65-<75	147	174	157
≥75	29	26	45
Age group 2 (years)			
	N	N	N
<65	339	369	369
≥65	176	200	202
Sex			
	N	N	N
Male	121	139	131
Female	394	430	440



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sWASO, subjective wake after sleep onset
Source: Applicant ISE Figure 20

Figure 46: Forest Plot of Change from Baseline for One Month – Age and Sex Subgroups (Full Analysis Set) Studies 303 and 304 for sWASO

Subgroup	PBO	LEM 5	LEM 10
Overall	N	N	N
	493	550	546
Age group 1 (years)			
	N	N	N
<65	320	356	355
≥65-<75	145	169	151
≥75	28	25	40
Age group 2 (years)			
	N	N	N
<65	320	356	355
≥65	173	194	191
Sex			
	N	N	N
Male	116	137	125
Female	377	413	421



Abbreviations: CI, confidence interval; LEM, lemborexant; PBO, placebo; sWASO, subjective wake after sleep onset
Source: Applicant ISE Figures 21

BMI: Similar to the above exploration for evaluation of efficacy by age subgroup, the Applicant presented efficacy findings according to BMI subgroups (<25 kg/m^2, 25 to 30 kg/m^2 and >30 kg/m^2). The forest plots were reviewed, and there were no clear differences in efficacy according to BMI; however, the subgroups were too small in number of patients to be conclusive (Source: Applicant's Integrated Summary of Efficacy (ISE), Figure 14).

Race: The forest plots were reviewed for efficacy by race. For sSOL, sSE, and WASO, patients of White and Black races showed similar improvements with LEM10. Improvements with LEM5 were less consistent. Results for Asian and Other race did not generally suggest efficacy; however, these subgroups were too small to provide meaningful aggregate results. Results were generally the same for 7 days and 1 month (Source: Applicant's ISE, Figures 14, 15, 18, 19, 22, 23).

8.1.3.1.4. Additional Efficacy Considerations

The primary efficacy endpoints for lemborexant clinical trials were measured after 30 days (or more) of nightly use. This is considered a strength for evaluating lemborexant for the treatment of chronic insomnia. Secondary and exploratory endpoints suggest that the effects of lemborexant at the beginning of treatment are similar to the effect with longer-term treatment. However, the efficacy of lemborexant in the as-needed setting was not evaluated.

As described above in the clinical reviewer comments, the inclusion and exclusion criteria for studies 303 and 304 were restrictive from a clinical "real world" perspective. Subjects with more than mild symptoms of anxiety and depression were excluded from the drug development program. The effectiveness of lemborexant in patients with major depressive disorder or generalized anxiety disorder was not tested. Psychiatric symptoms are commonly comorbid with insomnia disorder, so it is unclear how the efficacy of lemborexant is affected by psychiatric comorbidity or psychiatric treatment.

Based on the proposed use of the drug product, it is expected that lemborexant will be generally used in the same manner it was studied. However, we anticipate the use of concomitant psychotherapy with lemborexant, given that therapies such as CBT-I are recommended as first-line treatments. The benefit of lemborexant can reasonably be expected to be achieved in this setting. Concomitant medication use (for insomnia or other medical/psychiatric disorders) was not well represented in the trial, and it is not clear how the efficacy of lemborexant will be affected by concomitant medication use.

Both higher and lower doses of lemborexant can be expected to be used in the postmarket setting (e.g., off-label to increase efficacy or minimize adverse reactions), as this practice is common for the prescription of drugs to treatment insomnia. For lower doses (e.g., lemborexant 2.5 mg nightly), the graphic overlay of efficacy and somnolence by dose (Figure 2) suggested that lower doses of lemborexant may exhibit some efficacy. However, the efficacy of lemborexant 10 mg is similar to lemborexant 15 mg. The label instructions can help mitigate potential consequences of common off-label practices by stating that the recommended dose of lemborexant is 5 mg, and that the dose can be increased to 10 mg to improve efficacy.

The elderly population (patients > 65 years of age) was well represented in the lemborexant drug development program, and efficacy results were generally consistent for elderly and non-elderly populations. Efficacy results by other subgroup populations were inconsistent, but the studies were not powered to detect meaningful differences in efficacy by subgroup.

8.1.3.2. Integrated Assessment of Effectiveness

The two adequate and well-controlled efficacy studies presented by the Applicant (Studies 303 and 304) provide substantial evidence of effectiveness for lemborexant for the treatment of insomnia. Results from analyses of primary and key secondary endpoints provide the principal evidence for effectiveness. The studies also provide evidence supporting the clinical meaningfulness of the improvements in sleep parameters; these secondary and exploratory endpoints included objective and patient-reported measures.

8.2. Review of Safety

8.2.1. Safety Review Approach

Overview:
The focus of this review is the safety of lemborexant for the treatment of adult patients with insomnia. This review focuses primarily on safety data submitted from phase 3 studies. Findings from phase 2 studies and select phase 1 studies are also included in the review as relevant to the understanding of safety. See Section 8.2.2 *Review of the Safety Database* for details.

Safety review issues identified during drug development as requiring particular attention included: somnolence (including middle of the night safety and next-day impairment), suicidal ideation and behavior, parasomnias (including complex sleep behaviors), cataplexy and potential cataplexy, fractures, falls, and abuse liability (including overdose, drug abuse potential, withdrawal, and rebound). See Section 8.2.5*, Analysis of Submission-Specific Safety Issues* for details.

8.2.2. Review of the Safety Database

Overview: The Applicant defined the safety population (Safety Analysis Set) as the group of subjects who received at least one dose of randomized study drug and had at least one postdose safety assessment. The Safety Analysis Set contains data from 3371 subjects, including 2835 subjects with sleep disorders (of whom 1847 received lemborexant, 714 received placebo, 11 received zolpidem immediate release 10 mg and 263 received zolpidem extended release 6.25 mg). An additional 512 healthy subjects, 16 subjects with hepatic impairment, and 8 subjects with renal impairment are included in the Safety Analysis Set. Approximately 40% of subjects enrolled in lemborexant clinical studies were elderly (age ≥65 years).

In total, the Applicant described 20 studies in their Summary of Clinical Safety: 16 were phase 1 studies evaluating single or multiple doses of lemborexant, (range: 1 – 200 mg) administered to healthy subjects, subjects with insomnia, and special safety populations. One phase 2 proof-of-concept/dose-ranging study was conducted and another phase 2 study in subjects with Alzheimer's disease and irregular sleep-wake rhythm disorder (ISWRD) is ongoing. Two phase 3 studies were conducted in subjects with insomnia disorder.

Table 57 groups the studies by subject population (e.g., insomnia disorder, non-insomnia sleep disorder, and subjects with no sleep disorders). Additional details for individual studies are described and tabulated in Section 7.1. Refer to Section 6 for additional information on phase 1 studies and Study 201. See Section 6.3.2.3 for food-effect findings and drug-drug interactions and Section 6.3.2.4, 8.2.8, and 14.4.3 for a detailed description of the driving safety study. The protocols for phase 3 studies are described in detail in Section 8.1. The relevant safety findings from phase 1, 2, and 3 are presented in this safety review.

Table 57: Studies Included in the Applicant's Summary of Clinical Safety (SCS), Grouped by Subject Population

Population	Study	Phase	Description	LEM Dose	N*
Insomnia Disorder	001 Part B	1	R, DB, PC, AC Single Dose Study to Assess the Safety, Tolerability, PK and PD of LEM in Otherwise Healthy Subjects With Primary Insomnia	LEM2.5 LEM10 LEM25 ZOL 10 PBO	13 10 12 11 12
	107	1	R, DB, PC 3-Way CO Study to Evaluate the Effect of LEM 5 mg and 10 mg on a Multiple Sleep Latency Test in Subjects With Insomnia Disorder	LEM5 LEM10 PBO	69
	201	2	MC, R, DC, PC, Parallel-Group, Bayesian Adaptive Randomization Design, Dose-Response Study of the Efficacy of E2006 in Adults and Elderly Subjects With Chronic Insomnia	LEM 1 mg-25 mg PBO	235 56
	303-CORE	3	6 Month MC, R, DB, PC Parallel-Group Study of the Safety and Efficacy of LEM in Adults ≥18 Years Old With Insomnia Disorder	LEM5 LEM10 PBO	323 323 325
	303-EXT		6 Month Extension of 303-CORE, Parallel-Group Study in Adults ≥18 Years Old with Insomnia Disorder	LEM5 LEM10	384 351
	304	3	Multicenter, R, DB, PC, AC, Parallel-Group Study of the Efficacy and Safety of LEM in Subjects 55 Years and Older With Insomnia Disorder	LEM5 LEM10 PBO ZOL ER 6.25	266 269 208 263
Non-insomnia sleep disorders	102	1	DB, PC, CO study of respiratory safety of LEM10 in Obstructive Sleep Apnea (OSA)	LEM10, PBO LEM25, PBO	39 39
	202	2	R, DB, PC, parallel-group study, with open-label extension of efficacy and safety of LEM in subjects with ISWRD and mild to moderate Alzheimer's disease	LEM2.5 LEM5 LEM10 LEM15 PBO	12 13 13 12 12
	001 Part A	1	R, DB, PC, AC Single Dose Study to Assess the Safety, Tolerability, PK and PD of LEM in Healthy Subjects	LEM 1 mg-200 mg PBO	64
	002	1	R, DB, PC Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and PK of LEM in Healthy Adult and Elderly Subjects	LEM2.5-LEM75 PBO	41 14

Population	Study	Phase	Description	LEM Dose	N*
Subjects with no sleep disorders	003	1	Two-Part, R, DB, PC, Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, PK and PD of LEM in Healthy Japanese and White Subjects	LEM2.5-25 PBO	24 8
	004	1	Open label drug interaction study	LEM10	58
	005	1	Open-label, CO, bioavailability study of LEM capsule versus tablet formulations in healthy subjects	LEM2.5 LEM10 LEM25	12 12 16
	007	1	Open-Label, Single-Dose Study to Determine the Metabolism and Excretion of [14C]E2006 in Healthy Male Subjects	LEM10	8
	008	1	Open-label, CO, food-effect study of LEM10 in healthy subjects	LEM10	24
	009	1	Single-Center, DB, PC, Single-Dose, 4-Period CO, Drug-Alcohol Interaction Study in LEM in Healthy Subjects	LEM10, PBO	32
	012	1	Drug-Drug interaction study	LEM10 plus drug	50
	102	1	R, DB, PC CO Study to Evaluate the Respiratory Safety of LEM in Adult and Elderly Healthy Subjects	LEM10, LEM25, PBO	49
	103	1	R, DB, 6-Way CO Study to Determine the Abuse Potential of Single Oral Doses of LEM Compared to ZOL, Suvorexant and PBO in Healthy, Non-Dependent, Recreational Sedative Users	LEM10,LEM20,LEM40 ZOL30 SUV40 PBO	36
	104	1	An Open-label, Parallel-Group Study to Evaluate PK of LEM and its Metabolites in Subjects With Mild and Moderate Hepatic Impairment (Stable hepatic impairment conforming to Child-Pugh classification A or B) Compared to Healthy Subjects	LEM10, Class A LEM10, Class B LEM10, Healthy	8 8 8
	105	1	An Open-label, Parallel-Group Study to Evaluate the PK of LEM and its Metabolites in Subjects With Severe Renal Impairment Compared to Healthy Subjects	LEM10, Renal LEM10, Healthy	8 8
	106	1	R,DB,PC, AC 4-Period CO Study to Evaluate the Effect of LEM versus PBO on Driving Performance in Healthy Adult and Elderly Subjects	LEM2.5 LEM5 LEM10 ZOP PBO	48

Population	Study	Phase	Description	LEM Dose	N*
	107	1	DB, PC, CO study of morning sleep propensity for 2 doses of LEM in subjects with insomnia disorder, including Flurazepam 30 mg. Single dose study	LEM5 LEM10 PBO	79
	108	1	R, DB, PC, AC 4 Period CO Study to Evaluate the Effect of LEM versus PBO and ZOL on Postural Stability, Auditory Awakening Threshold, and Cognitive Performance in Healthy Subjects ≥55 years of age	LEM5 LEM10 ZOL PBO	63

*N refers to number of subjects by Arm enrolled in the study
Abbreviations: AC, active controlled; CO, cross-over DB, double blind; ER, extended release; ISWRD, Irregular Sleep-Wake Rhythm Disorder, LEM, lemborexant; MC, multicenter; PC, placebo controlled; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; R, randomized; SUV, suvorexant; ZOL, zolpidem
Source: Clinical Reviewer modified table from the ISS 120-Day Update Table 1.

Controlled Data: The phase 3 controlled safety data supporting this application include the first six months of E2006-G000-303 (also referred to by the Applicant as "Study 303", "Study 303-Core, or "Study 303 Period 1") and E2006-G000-304 (also referred to as "Study 304"). Study 303-Core and Study 304 were multicenter, randomized, double-blind, placebo-controlled studies of LEM5 and LEM10 in adults with insomnia disorder and are described in more detail in Section 8.1. For this safety review, Study 303-Core and Study 304 were evaluated independently as well as within several pooled analyses, as described below in Pooling Safety Data under Section 8.2.2.1.2.

Uncontrolled Data: The phase 3 lemborexant drug development program included non placebo-controlled data in Study E2006-G000-303 that was considered for this review. Refer to Section 8.1.1 for a detailed description to the E2006-G000-303 research design. Briefly, Study 303-Core included a six-month extension phase, referred to as 303-EXT, or Period 2. After the first six months of Study 303-Core, subjects in the LEM5 or LEM10 arm continued on their current dose of lemborexant without changes, and subjects in the placebo arm were re-randomized to either LEM5 or LEM10. Data from the 303-EXT were included within several of the pooled datasets described below. 303-EXT is important for the safety review because it provides safety data through up to 12 months of exposure for some subjects. The lack of placebo control in 303-EXT is a limitation; however, data from subjects who were randomized from placebo to LEM5 or LEM10 are also potentially useful because they were blinded to treatment at all stages of 303, including 303-EXT.

Other Studies in Subjects with Insomnia Disorder: 001B, 107, and 201 were conducted in individuals with insomnia disorder. Study 107 was a phase 1 study using single doses of LEM5 and LEM10 to test next-morning residual sleepiness on a modified Multiple Sleep Latency Test (MSLT) in subjects with insomnia disorder, and therefore provides useful safety information for single indicated doses of lemborexant. Safety data from Studies 001B and 201 were reviewed but are considered secondary sources of safety data because they both evaluated lemborexant

doses higher and lower than the to-be-marketed doses (range: 1 to 200 mg). Therefore, it could be misleading to extrapolate the mean findings from LEM1 to LEM200 to the proposed doses of 5 and 10 mg. See Sections 6, 8.2.8, and 8.1 for additional details on Studies 001B, 107, and 201, respectively.

Studies in Other Sleep Disorders: The safety data from Study 102 evaluating respiratory safety in obstructive sleep apnea (OSA) is reviewed in detail in *Specific Safety Studies* (Section 8.2.8). Study 202 was conducted in individuals with Alzheimer's disease who also had ISWRD. Because the focus was ISWRD, it is not clear if these findings can be extrapolated to individuals with a DSM-5 diagnosis of insomnia disorder. Also, Study 202 was still ongoing during the final ISS database submission. Therefore, Study 202 is not presented in detail for this safety review. However, the data available at the time of the 120-Day safety update are included within the All Sleep Disorders Pool and the Applicant's combined phase 2 and 3 safety dataset, which is considered within this review of safety.

Other Studies in Healthy Subjects or Other Populations: Several phase 1 studies were considered individually for this review: Studies 102 (respiratory safety), 103 (abuse potential), 104 (hepatic impairment), 105 (renal impairment), 106 (driving safety), 107 (morning sleep propensity), and 108 (postural stability and next day impairment). See Section 6.3 and Section 8.2.8 for details. Other phase 1 studies (e.g., pharmacokinetic or pharmacodynamic studies) that did not contribute clinically relevant findings were not described in this safety review.

Comparator Arm: Several studies in the lemborexant drug development program included an active comparator arm using zolpidem, zolpidem ER, or zopiclone (e.g., Studies 001B, 106, 108, and 304). Study 103 was an abuse potential study that included high-dose zolpidem. Refer to Section 7.1, Table 57, and Section 8.2.5.9 for details. The only phase 3 study with an active comparator was Study 304, which included a zolpidem ER treatment arm.

120-Day Safety Update: The Applicant submitted the 120-day safety update of the ISS on April 19, 2019. The Applicant reports the cutoff date for the ISS was September 14, 2018, and the cutoff date for the 120-day safety update was January 11, 2019. The 120-day safety update included no new subjects enrolled compared to the original ISS, but included longer follow-up for many subjects in 303-EXT, see below. The Applicant noted that no new or unexpected safety findings were identified in the 120-day safety update.

The Applicant reported that the 120-day ISS included the following:

- New data for 243 subjects in the E2006-G000-303 extension study
- New data for 20 subjects in the phase 2 trial in Alzheimer's disease, E2006-G000-202, who are continuing in an extension period
- One additional subject presented in the LEM5 group compared to the ISS for Study E2006-G000-303. This subject received placebo (PBO) in Period 1 and, at the time of the ISS cut-off, had not been assigned a dose or had a study visit in Period 2. After the ISS

cut-off, the subject was assigned LEM5 in Period 2 and is now included in the LEM5 group.

Clinical Reviewer Comments*: The safety analysis set defined by the Applicant is standard and acceptable for insomnia drug development programs. The appropriateness and relevance of the safety population is described below.*

8.2.2.1. Relevant Characteristics of the Safety Population

8.2.2.1.1 Overall Exposure

The overall exposure for the lemborexant drug development program was 3371 subjects: 2835 with sleep disorders (1847 received lemborexant, 714 received placebo, 11 received zolpidem immediate release, 263 received zolpidem ER; 512 healthy controls, 16 hepatic impairment, and 8 renal impairment). The overall exposure meets the ICH E1A recommendation for the extent of population exposure to evaluate the safety of drugs intended for the long-term treatment of non-life-threatening diseases.

Table 58 provides a summary of lemborexant exposure by duration and dose in the phase 3 studies. Subjects were counted in each applicable exposure category. The Applicant defined one month as ≥23 days; 3 months as ≥83 days; 6 months as ≥173 days; 9 months as ≥263 days; 12 months as ≥353 days. The duration of exposure of study drug was defined as the number of days between the date the subject received the first active dose of study drug during the corresponding treatment period and the date the subject received the last active dose of study drug, inclusive. For the Phase 3 Pool, the mean duration of exposure in days (SD) was 174.5 (144.7) and 164.0 (142.0) for LEM5 and LEM10, respectively, and 110.5 (74.0) for placebo (Source Applicant's 120-Day Update, Table 2). In phase 3 studies, total exposure was 340.2 and 315.2 patient-years for LEM5 and LEM10, respectively, 158.6 patient-years for placebo, and 21.0 patient-years for zolpidem.

Table 58: Extent of Lemborexant Exposure by Time in the Phase 3 Pool

Days of Exposure	Placebo (N=528)	Lemborexant 5 mg (N=713)	Lemborexant 10 mg (N=705)	Total (N=1418)
≥ 1 day	528 (100)	713 (100)	705 (100)	1418 (100)
≥ 7 days	519 (98.3)	706 (99.0)	692 (98.2)	1398 (98.6)
≥ 1 month	506 (95.8)	693 (97.2)	677 (96.0)	1370 (96.6)
≥ 3 months	292 (55.3)	405 (56.8)	380 (53.9)	785 (55.4)
≥ 6 months	262 (49.6)	373 (52.3)	335 (47.5)	708 (49.9)
≥ 9 months	0	243 (34.1)	213 (30.2)	456 (32.2)
≥ 12 months	0	230 (32.3)	204 (28.9)	434 (30.6)

Abbreviation: SD, standard deviation
Source: Modified from Applicant's 120-Day Update, Table 2

Extent of Exposure to Lemborexant in Other Studies:

1. **Obstructive Sleep Apnea (OSA)**, Study 102 randomized 39 subjects with mild OSA, 38 of whom received both placebo and LEM10. The mean exposure to LEM10 was 7.9 days (range: 1 to 10 days). See Section 8.2.8 *Specific Safety Studies* for additional details on Study 102.

2. **Alzheimer's Disease,** Study 202 was a randomized, double-blind, placebo-controlled study in subjects with mild to moderate Alzheimer's disease and ISWRD. As of the Applicant's 120-Day Update, 50 subjects have been exposed to lemborexant in Study 202 (12 to LEM2.5, 13 to LEM5, 13 to LEM10 and 12 to LEM15). All subjects received study drug with a median exposure of 28 days for all groups. A total of 50 subjects were exposed to lemborexant for at least 26 days.

3. **Hepatic Impairment,** Study 104 enrolled 24 subjects (8 with mild hepatic impairment, 8 with moderate hepatic impairment, and 8 matched healthy controls); each received a single dose of LEM10. See Section 8.2.8 *Specific Safety Studies* for additional details.

4. **Renal Impairment**, Study 105 enrolled 16 subjects (8 subjects with severe renal impairment and 8 matched healthy controls); each received a single dose of LEM10. See Section 8.2.8 *Specific Safety Studies* for additional details.

5. **Healthy Subjects:** The Single-Dose Pool includes 538 healthy subjects who received a single dose of lemborexant. LEM10 was the most frequently administered single dose (263 subjects), but doses ranged from 1 to 200 mg. In the Multiple-Dose Pool, 133 subjects were exposed at least 6 days and 131 subjects were exposed for at least 14 days (70 to LEM10; 38 to LEM5).

Clinical Reviewer Comments*: The Applicant's exposure exceeds the ICH E1A guidelines, which recommend six months exposure for 300 patients and 12 months exposure for 100 patients. This is a strength of the application. Characteristics of the safety population are described below.*

8.2.2.1.2 Pooling Safety Data and Characteristics of the Safety Population

Overview: In the Summary of Clinical Safety (SCS), The Applicant reported data from several pooled datasets, including subjects with insomnia in phase 3 studies (Phase 3 Pool), all subjects with insomnia (All Insomnia Pool), all subjects with sleep disorders (All Sleep Disorders Pool), a Single-Dose Pool, and a Multiple-Dose Pool. The Applicant also presented data on special safety populations. In addition, the clinical review team considered the phase 2 and 3 safety database submitted by the Applicant with the 120-Day safety update.

The primary pooling strategies are described below, as well as demography of the pools.

Combined Phase 2 and 3 Safety Database: A combined database of all phase 2 and phase 3 safety data was the submitted with the 120-Day Safety Update. Although this was not identified

as a primary review pool by the Applicant, clinical reviewer-generated findings were used in the safety review when investigating rare events, such as parasomnia, or when considering a wider range of doses (LEM1-LEM25). This database uniquely includes zolpidem 10 mg data. The total number of subjects in the combined phase 2 and 3 safety database was 2472. Of these, 1333 subjects received LEM5 or LEM10. The demography of this database are reported in Table 59. Of note, some subjects from Study 303-EXT were counted twice, once under placebo (from the first 6 months of the study) and once under LEM5 or LEM10 (in the second 6 months of the study, after re-randomization to receive LEM5 or LEM10).

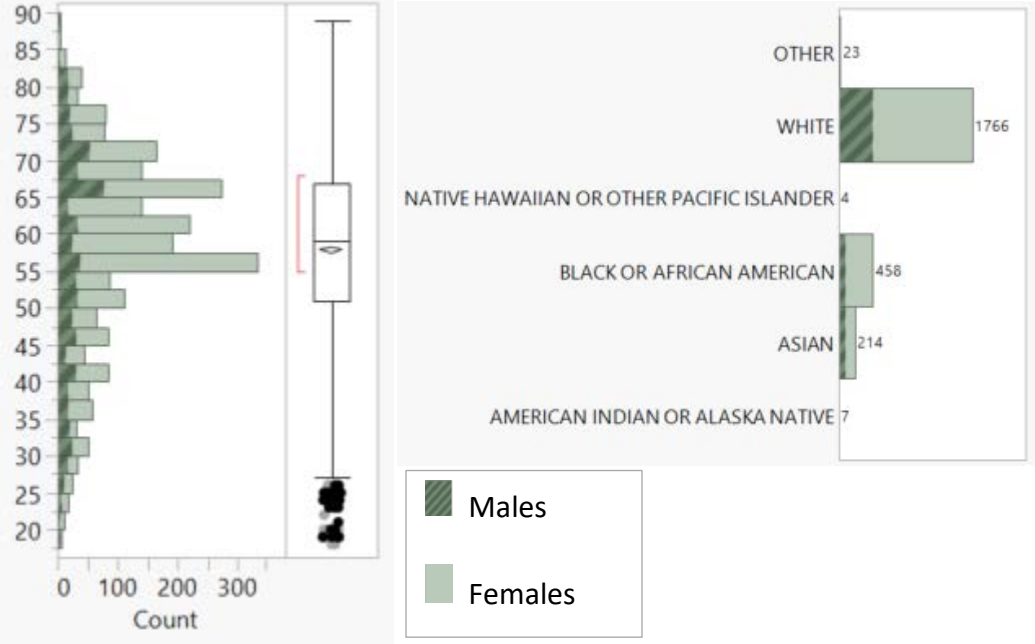
Table 59: Demography - Combined Phase 2 and 3 Database

	LEM1/ LEM2.5	LEM5	LEM10	LEM15/ LEM25	ZOL ER 6.25	ZOL10	PBO
N(%)	84 (3.4)	654 (26.5)	679 (27.5)	130 (5.3)	263 (10.6)	11 (0.4)	651 (26.3)
Age(%)							
≤ 39	15 (17.9)	65 (9.9)	64 (9.4)	37 (28.5)	0	4 (36.4)	86 (13.2)
40-64	46 (54.8)	361 (55.2)	381 (56.1)	74 (56.9)	143 (54.4)	7 (63.6)	352 (54.1)
65+	23 (27.4)	228 (34.9)	234 (34.5)	19 (45.6)	120 (45.6)	0	213 (32.7)
Sex							
Female	52 (61.9)	484 (74.0)	507 (74.7)	79 (60.8)	226 (85.9)	5 (45.5)	480 (73.7)
Male	32 (38.1)	170 (26.0)	172 (25.3)	51 (39.2)	37 (14.1)	6 (54.5)	171 (26.3)
Race							
AI, AN	0	2	4 (0.6)	1 (0.8)	0	0	0
Asian	3 (3.6)	68 (10.4)	67 (9.9)	5 (3.8)	5 (1.9)	1 (9.1)	65 (10)
Black/AA	20 (23.8)	109 (16.7)	110 (16.2)	29 (22.3)	80 (30.4)	2 (18.2)	108 (16.6)
NH, PI	0	1 (0.2)	0	0	2 (0.8)	0	1 (0.2)
White	61 (72.6)	467 (71.4)	492 (72.5)	94 (72.3)	173 (65.8)	8 (72.7)	471 (72.4)
Other	0	7 (1.1)	6 (0.9)	1 (0.8)	3 (1.1)	0	6 (0.9)

Abbreviations: AA, African American; AI, American Indian, AN, Alaska native; ER, extended release; ISS, integrated summary of safety; LEM, lemborexant; NH, native Hawaiian; PBO, placebo; PI, Pacific Islander; ZOL, zolpidem
Source: Clinical Reviewer generated table from Applicant's ISS database (120-day update)

Table 59 and Figure 47 display the distribution of subjects in the combined phase 2 and 3 safety database. At the to-be-marketed doses, approximately one-third of subjects were 65 or older, three quarters were female, and approximately 16% of subjects were black. Such representation seems reasonable considering the demographics of the overall US population. In In Figure 47, the green stripes represent males and the solid green bars represent females. Note the relatively small percentage of males for each group.

Figure 47: Distribution of Age and Race in the Combined Phase 2 and 3 Database



Abbreviation: ISS, integrated summary of safety
Source: Clinical Reviewer figure generated from the Combined Phase 2 and 3 database

Phase 3 Pools: Two pools from phase 3 studies were considered for this review, the "Phase 3 Pool" and the "Phase 3 30-day Pool."

The **Phase 3 Pool** contains all the data from the two phase 3 studies, E2006-G000-303, including 303-EXT, and E2006-G000-304. The Phase 3 Safety Pool includes data from all subjects who took at least one dose of study drug. All subjects in this pool had a DSM-5 diagnosis of insomnia disorder, no other current sleep disorders, and no more than mild depressive or anxiety symptoms at screening. Note that this pool includes subjects re-randomized in the 303-EXT. As such, the placebo subjects only continued to month 6 during Study 303 compared to a possible 12 months exposure for LEM5 and LEM10. The placebo subjects in the study were counted twice, once under placebo (Study 303-Core) and once under LEM5 or LEM10 in 303-EXT. For the clinical safety review, all results for the Phase 3 Pool are from the 120-Day safety update database. Table 60 lists the numbers of subjects by treatment arm in the Phase 3 Pool.

Table 60: Lemborexant Studies Included in the Phase 3 Pool, by Treatment Arm

Clinical Trials	Placebo (n=533)	LEM5 (n=713)	LEM10 (n=705)	ZOL ER 6.25mg (n=263)
E2006-G000-303-Core	325	323	323	-
E2006-G000-303-EXT	-	133	125	-
E2006-G000-304	208	266	269	263

Abbreviations: ER, extended release; LEM, lemborexant; ZOL, zolpidem
Source: Modified from Applicant's 120-Day Safety Update, Table 1

Table 61 shows the demography of the Phase 3 Pool. The overall average age was 59.3 (SD 11.7) years; 36.5% of this group was elderly.

Table 61: Demography – Phase 3 Pool, by Treatment Arm

	PBO (N=528) n (%)	ZOL ER (N=263) n (%)	LEM5 (N=713) n (%)	LEM10 (N=705) n (%)	LEM Total (N=1418) n (%)
Age(%)					
Mean	58.0	64.3	57.9	58.6	58.2
SD	12.4	7.12	12.4	12.3	12.4
<65 n,%	346 (65.5)	143 (54.4)	467 (65.5)	460 (65.2)	927 (65.4)
65+ n,%	182 (34.5)	120 (45.6)	246 (34.5)	245 (34.8)	491 (34.6)
Sex					
Male	125 (23.7)	37 (14.1)	186 (26.1)	176 (25.0)	362 (25.5)
Female	403 (76.3)	226 (85.9)	527 (73.9)	529 (75.0)	1056 (74.5)
Race					
White	387 (73.3)	173 (65.8)	516 (72.4)	516 (73.2)	1032 (72.8)
Black/AA	74 (14.0)	80 (30.4)	98 (13.7)	93 (13.2)	191 (13.5)
Asian	61 (11.6)	5 (1.9)	89 (12.5)	88 (12.5)	177 (12.5)
Other	6 (1.1)	5 (1.9)	10 (1.4)	8 (1.1)	18 (1.3)

Abbreviations: AA, African American; ER, extended release; ISS, integrated summary of safety; LEM, lemborexant; PBO, placebo; ZOL, zolpidem
Source: Clinical Reviewer Modified Table modified from Applicant's 120-day Update, Table 3.1.1

Phase 3 30-Day Pool: The Agency determined that the primary safety population for lemborexant label's adverse events table would be limited to data from the first 30-days of Phase 3 Pool, to avoid bias related to combing two studies of different study durations (12 months for studies E2006-G000-303 and 1 month for E2006-G000-304). Therefore, the Phase 3 30-day Pool includes only the first 30 days of data for studies E2006-G000-303 and E2006-G000-304. The Applicant was informed of this decision and submitted data for the first 30 days of Studies 303 and 304 to create the Phase 3 30-day Pool. Table 62 shows the number of subjects by treatment arm in the Phase 3 Pool, and Table 63 shows their demography.

Table 62: Lemborexant Studies Included in the Phase 3 30-Day Pool, by Treatment Arm

Clinical Trials	Placebo (n=528)	LEM5 (n=585)	LEM10 (n=588)	ZOL ER 6.25mg (n=263)
E2006-G000-303 Core	320	319	319	-
E2006-G000-304	208	266	269	263

Abbreviations: ER, extended release; LEM, lemborexant; ZOL, zolpidem
Source: Study 303 and 304 CSR

Table 63: Demography – Phase 3 Safety Pool

	PBO (N=528) n (%)	ZOL ER 6.25 (N=263) n (%)	LEM5 (N=580) n (%)	LEM10 (N=582) n (%)	LEM Total (N=1162) n (%)	Combined Total, N=1953 n (%)
Age(%)						
Mean	58.0	64.3	58.5	59.1	58.8	59.3
SD	12.4	7.1	12.0	11.9	12.0	11.7
<65 n(%)	346 (65.5)	143 (54.4)	375 (64.7)	377 (64.8)	752 (64.7)	1241 (63.5)
65+ n(%)	182 (34.5)	120 (45.6)	205 (35.3)	205 (35.2)	410 (35.3)	712 (36.5)
Sex						
Male	125 (23.7)	37 (14.1)	144 (24.8)	135 (23.2)	279 (24.0)	441 (22.6)
Female	403 (76.3)	226 (85.9)	436 (75.2)	447 (76.8)	883 (76.0)	1512 (77.4)
Race						
White	387 (73.3)	173 (65.8)	418 (72.1)	427 (73.4)	845 (72.7)	1405 (71.9)
Black/AA	74 (14.0)	80 (30.4)	91 (15.7)	86 (14.8)	177 (15.2)	331 (16.9)
Asian	61 (11.6)	5 (1.9)	63 (10.9)	63 (10.8)	126 (10.8)	192 (9.8)
Other	6 (1.1)	5 (1.9)	8 (1.4)	6 (1.0)	14 (1.2)	25 (1.3)

Abbreviations: AA, African American; ER, extended release; ISS, integrated summary of safety; LEM, lemborexant; PBO, placebo; ZOL, zolpidem
Source: Clinical Reviewer Modified Table modified from Applicant's Table 3.1.1., ISS Month 1 Safety

All Insomnia Pool: The Applicant's All Insomnia Pool, which is broader than the Phase 3 Pool discussed above, consists of all studies with subjects with insomnia disorder (001 Part B, 107, 201, 303 and 304). The medical history in this subject population was reported as broad and varied, and may be more representative of the broader general population who may be prescribed the drug. The All Insomnia Pool includes a wide range of dosage for lemborexant (1, 2.5, 5, 10, 15, and 25 mg). The combined total subjects was 2,461 (1848 subjects in lemborexant arms and 714 subjects in the placebo arm). The mean age was 57.4 years (SD 12.8), the minimum age was 18, and the maximum age was 88. 67.6% of the subjects were younger than age 65, and 26.5% were 65 years or older.

All Sleep Disorders Pool: The All Sleep Disorders Pool consists of all subjects in the lemborexant drug development program with any diagnosis of a sleep disorder, including Study 102 in subjects with mild OSA and ISWRD in Alzheimer's disease (Study 202). The Applicant-conducted analyses were reviewed for the All Sleep Disorders Pool and did not vary significantly in results compared to the All Insomnia Pool. Given that this pool includes all subjects in the All Insomnia Pool as well as subjects with disorders other than insomnia, including patients with obstructive sleep apnea and Alzheimer's disease, this pool was not considered clinically meaningful for this clinical safety review. However, when relevant, we considered results from the All Sleep Disorders Pool separately to assess for safety signals that may have not been captured in the All Insomnia Pool.

Pooled QTc Report: The Applicant's Pooled QTc Report provides concentration effect analyses of combined data from Studies 002 and 003; there were no dedicated QT studies. Results from the QTc report and the internal QT analysis are reviewed in Section 8.2.4.9.

Clinical Reviewer Comments: *The Applicant's rationale for defining the Phase 3 Pool, the All Insomnia Disorders Pool, and the Pooled QTc Report are acceptable. Theses pooled databases facilitate safety analyses for different patient populations and dose ranges. Other databases were considered less meaningful for the safety review and are included only when relevant.*

As described above, the pooling strategies also have limitations, including the grouping of studies with treatment durations ranging from 1 day to 12 months within specific pools, the wide range of lemborexant dosages, from 1 mg to 200 mg, counting placebo subjects twice in Study 303-EXT, and that the maximum duration of time on placebo is half (6 months) the maximum duration on LEM5 and LEM10 (12 months). Therefore, although the pooled databases are considered important for reviewing the overall safety of lemborexant, the safety data from these pools must be interpreted within the limitations and potential bias described above. For this reason, a Phase 3 30-Day Pool was requested by the Applicant to be used for the basis of label and the adverse event table.

8.2.2.1.3 Adequacy of the Safety Database and Clinical Reviewer Comments

The database includes safety data for a range of lemborexant doses (1 mg to 200 mg), a range of exposure durations (1 day to 12 months), a range of ages for adult subjects (18 to 88 years), an adequate number of elderly subjects (e.g., 36.5% in phase 3 studies), and an adequate number of subjects exposed to lemborexant (1847 subjects with insomnia disorder received lemborexant). The durations of exposure to LEM5 or LEM10 are adequate (e.g., 708 subjects with insomnia exposed to LEM5 or LEM10 for 6 months or greater), which is greater than the minimum durations specified in the ICH E1A guideline recommendations.

One limitation of the safety database relates to special populations and safety studies. For example, the respiratory safety study in the lemborexant program only included patients with mild OSA. No patients with COPD or moderate to severe OSA were considered. There is no data on pregnant or lactating women. There is no data in pediatric populations.

Another limitation of the safety database was that the patient population is not entirely reflective of the target US patient population. For example, in the Phase 2 and Phase 3 Pool, 74.3% of subjects were female. Moreover, the numbers of patients in various subgroups (i.e., age, sex, race) were not large enough to draw conclusions on differences in safety findings by subgroup (this is typical of most applications).

Clinical Reviewer Comments*: The Applicant submitted numerous safety studies in phases 1, 2, and 3. Additional studies in patients with Alzheimer's disease and severe renal impairment inform the safety of lemborexant in special populations. However, several safety populations were not represented in the safety analysis set. The Applicant did not include patients with*

severe hepatic impairment, which is a limitation that will be reflected in the label. Similarly, the Applicant only studied mild OSA, and the effects of lemborexant in moderate to severe OSA and COPD are unknown; these limitations will be reflected in the label. Pediatric studies were not planned based on prior discussion with the Agency and the Applicant's request for a full waiver from the requirements of the Pediatric Research Equity Act (PREA). Maternal, fetal, and infant outcomes of women exposed to lemborexant were not studied, and the Agency will issue three related post-marketing requirements (a pregnancy registry, a case-control or retrospective cohort study to assess infants, and a lactation study, see Section 13.1, Post Marketing Requirements). See Sections 8.1, 8.2.5 and Section 8.2.8 for additional clinical reviewer comments on study design strengths and limitations.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was performed by the FDA JumpStart team. There were no anomalies detected in Study 303-Core. The assessment of 303-EXT, 304, and the ISS database identified several duplicate treatment period date/time variables that required removal to be used in JMPClinical, the primary data analysis review application used by the clinical review team.

The Applicant planned to submit case narratives for the following situations: deaths, serious adverse events, early discontinuations, events related to pregnancy/breastfeeding, medication errors, suicidal ideation and behavior, Hy's Law, overdoses, complex sleep-related behaviors, road traffic accidents, select AEs of interest (cataplexy, potential cataplexy, falls, seizures, sleep paralysis, and events related to potential abuse liability).

The safety data were organized through hyperlinks, allowing for a full review within the expectations set by Good Review Management Principles (GRMP). There were no major issues with safety data quality and no major amendments to the NDA were necessary during the review cycle. The Applicant was responsive to information requests and other communications during the review.

The Office of Scientific Investigations (OSI) conducted inspections of three clinical sites (PIs: Drs. Garcia-Borreguerro, Harper, and Safirstein). These sites were selected based on factors including relatively large enrollment and a high subject dropout rate. The conclusion of the OSI review team was that the studies (303 and 304) appeared to have been conducted adequately and the data generated by these sites appeared acceptable in support of the application.

Translation of Verbatim Terms to Preferred Terms: The adae.xpt datafile for the phase 3 studies was examined for the accuracy of translation from verbatim terms (provided by study personnel) to preferred terms listed under AEDECOD. Each unique verbatim term (1664) was viewed for the combined adae.xpt files for E2006-G000-303 and E2006-G000-304 to determine if the preferred term accurately captured the clinical event described by the verbatim term. Where replacements were indicated, the original verbatim term was deleted in replaced.

Where terms were considered missing, the additional preferred term(s) were added. Most updates were additions. Examples are provided in Table 64. Missing the MedDRA term "fall" occurred on several occasions, for example. Therefore, recoded databases were utilized to consider the safety of lemborexant for insomnia disorder, when relevant.

Table 64: Examples of Review Team Updates to Preferred Terms for Safety Review

Type of Change	Verbatim term from Applicant	Preferred term provided by Applicant	Change made by review team
Addition	Subject got rib bone fracture from falling down	Rib fracture	Added term *Fall*
Addition	Confusion (Secondary to Accidental IP Overdose)	Confusional State	Added term *Accidental Overdose*
Replacement	Leaden heaviness after awakening which disappears after getting up	Discomfort	Deleted original preferred term and replaced with *Parasomnia*

Grouping of Preferred Terms: To better assess for the presence and magnitude of safety signals, the clinical review team grouped related preferred terms. Pertinent examples are listed in Table 65.

Table 65: Grouping Terms and Related Preferred Terms

Grouping Term	Preferred terms included in grouping term
Confusional State	Confusion, delirium, altered mental status, disorientation, coma
Dizziness	Fall, dizziness, balance disorder, gait disturbance, difficulty walking
Infections	URI, cold, rhinitis, upper resp tract infection, flu-like illness
Abnormal Dreams	Nightmare or abnormal dreams
Parasomnia	Sleep paralysis, hypnagogic hallucination, parasomnia, exploding head syndrome
Somnolence	Somnolence, lethargy, fatigue, sedation

Abbreviation: URI, upper respiratory infection
Source: Clinical Reviewer generated table from the combined 303 and 304 adae.xpt file

Categorization of Adverse Events (AEs)

The Applicant used standard procedures to collect, code, and analyze the incidence of AEs for all studies described in the ISS. Adverse events were collected beginning from the time the subject signed the study informed consent form through the last study visit. Serious adverse events were collected for 28 days after the last dose of study drug. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 for most studies, or the most recent version available at the time of the study.

Treatment Emergent Adverse Events (TEAEs): The Applicant classified adverse events as TEAE differently across different studies (see Table 66 below). The TEAE definitions appeared to be

appropriate for the studies based on their designs. Subjects with two or more of the same preferred term were counted only once.

Table 66: Applicant Rules for Coding AEs as TEAEs

Study	Timing of AE for Counting as TEAE
Crossover studies (Studies 005, 008, 009, 102, 103, 106, 107, and 108)	Up to 14 days post dose or attributed to the dosing in the next treatment period, whichever was earlier
Phase 2 and 3 studies	The AE had an onset date on or after the first dose of study drug in the Randomization Phase, up to and including 14 days after the last dose of study drug.
Studies 004 and 0012	Started at or after administration of LEM alone
Other Phase 1 Studies	Started at or after administration of LEM or PBO; present before but increased in severity after administration of LEM/PBO; occurred before EOS or within 14 days

Abbreviations: AE, adverse event; EOS, end of study; LEM, lemborexant; PBO, placebo; TEAE, treatment-emergent adverse event
Source: Summarized from Applicant's Summary of Clinical Safety

Serious adverse events:
A treatment-emergent serious adverse event was defined by the Applicant as a serious adverse event with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug.

Data sources used to review serious adverse events included the Applicant's Integrated Summary of Safety (ISS), individual study body reports, study and ISS databases, and the Applicant's narrative summaries.

The Applicant categorized AEs as serious adverse events based on the legal definition: death, life-threatening events, requiring inpatient hospitalization/prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or a congenital anomaly/birth defect in the child of a subject who was exposed to the study drug.

Other significant AEs: Other significant AEs identified by the Applicant included pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; treatment-emergent significant laboratory abnormalities.

AEs of special interest: The Applicant identified select adverse events of interest to the proposed indication:

- Cataplexy and Potential Cataplexy: TEAEs with MedDRA preferred terms and any additional events identified by an investigator as potential cataplexy in the electronic Case Report Form (eCRF). Per agreement, "fall" was also included in the potential cataplexy MedDRA PT list. An independent Adjudication Committee, comprised of 3 physicians with expertise in sleep and seizure, was employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure.

Additional events identified by an investigator as potential cataplexy in the eCRF were also sent for adjudication

- Fall: TEAEs with MedDRA preferred terms of "Fall"
- Seizure: TEAEs with MedDRA preferred terms belonging to standardized MedDRA query (SMQ) of "Convulsion" (Narrow Terms)
- Sleep paralysis: TEAEs with MedDRA preferred terms of "Sleep paralysis"
- Somnolence: TEAEs with MedDRA preferred terms of "Somnolence"
- Events potentially related to abuse liability

After reviewing the Applicant's integrated summary of safety and considering known safety concerns from the other drug in the class, suvorexant, and other hypnotic drugs, the review team identified several other adverse events of interest. For example, sleep paralysis was expanded to include other MedDRA terms associated with parasomnias, including complex sleep behaviors. Suicidal thoughts and ideation were included as AEs of interest because the potential for increased risk was described in another drug in the same class as lemborexant.

It was noted that only one AE of seizure was reported in the drug development program (Subject (b) (6), LEM25 from Study 201). As such, the clinical team did not include seizure as an AE of special interest for this safety review.

The Agency did not issue clinical holds for any studies conducted as part of this development program.

Routine Clinical Tests

Routine clinical tests were performed. Vital signs included diastolic and systolic blood pressure, heart rate, respiratory rate, temperature, and weight. Laboratory assessments were collected at Screening, Baseline, at various time points during the treatment periods of studies, at the end of the study/treatment visit, and as applicable, at follow-up and unscheduled visits. For most studies, 12-lead ECGs were obtained at Screening, Baseline, at various time points during treatment periods, at the end of treatment (EOT) visit, and as applicable, at follow-up/ end of study (EOS) and unscheduled visits.

Other cardiac assessments included Holter monitoring for 24 hours predose and 24 hours post dose in single-dose Study 001 Part A, as well as 30 minutes predose and 12 hours postdose for each night of dosing in multiple-dose Study 002.

In Study 002 and Study 003, a continuous ECG signal was obtained at predose Baseline and on the first and last nights of dosing. From the continuous ECG signal, approximately 10 minutes of data were extracted at times coinciding with the time that each PK sample was obtained. These extracts were then analyzed for the QT assessment.

Details of the timing and collection of routine clinical tests are listed in Section 8.1.1 for Studies 303 and 304.

8.2.4. Safety Results

8.2.4.1. Deaths

No deaths occurred during the drug development program. No healthy subjects or subjects with sleep disorders experienced any AE leading to death in single or multiple-dose studies.

8.2.4.2. Serious Adverse Events

Because the durations of the phase 3 studies (303 and 304) differed, simple pooling of the serious adverse events from both studies would not be appropriate. Thus, an initial analysis of serious adverse events was restricted to the first 30 days of both studies. In this analysis, there were only two treatment-emergent serious adverse events in lemborexant-treated subjects: a cerebrovascular accident and viral gastroenteritis. As single events, these are difficult to interpret.

In order to consider all of the treatment-emergent serious adverse events from the phase 3 studies, they were tabulated and expressed as events per 100 patient-years (Table 67). Serious adverse events reported in two or more lemborexant-treated subjects are shown. The overall frequencies of serious adverse events in phase 3 studies were 2.8% and 2.3% in lemborexant 5 and 10 mg groups, respectively, and 0.9% in the placebo group.

Table 67: Treatment-Emergent Serious Adverse Events Occurring in ≥2 Subjects Receiving Lemborexant in Phase 3 Pool – Events per 100 Patient-years.

	Lemborexant			Placebo	Zolpidem 6.25 mg	Risk Difference
	5 mg	10 mg	Both			
Exposure (patient-years)	**340.2**	**315.2**	**655.3**	**158.6**	**21.0**	
Infection, all	4 (1.2)	1 (0.3)	5 (0.8)	2 (1.3)	1 (4.8)	-0.5
Fracture, all	3 (0.9)	2 (0.6)	5 (0.8)	2 (1.3)	(0)	-0.5
Osteoarthritis	1 (0.3)	3 (1)	4 (0.6)	(0)	(0)	0.6
Breast cancer	1 (0.3)	1 (0.3)	2 (0.3)	(0)	(0)	0.3
Arrhythmia (atrial fibrillation, extrasystoles)	1 (0.3)	1 (0.3)	2 (0.3)	(0)	(0)	0.3
Chest pain (non-cardiac or unknown)	2 (0.6)	0 (0)	2 (0.3)	(0)	1 (4.8)	0.3
Diabetic neuropathy	2 (0.6)	0 (0)	2 (0.3)	(0)	(0)	0.3
Gastroenteritis	2 (0.6)	0 (0)	2 (0.3)	(0)	(0)	0.3
Fall	1 (0.3)	1 (0.3)	2 (0.3)	(0)	(0)	0.3
Acute coronary syndrome*	1 (0.3)	1 (0.3)	2 (0.3)	(0)	1 (4.8)	0.3

*Includes angina pectoris, coronary artery disease, acute myocardial infarction
Risk difference represents lemborexant (both) minus placebo. Subjects with two or more AEs with the same preferred term are counted only once for that preferred term.
Source: Analyses from 120-day Safety Update: \\0012\m5\datasets\iss-phase-2-3\analysis\adam\datasets\adae.xpt and adsl.xpt

The most common serious adverse events were serious infections and fractures; however, rates per 100 patient-years were similar in patients randomized to lemborexant and placebo. Other serious adverse events in the table are difficult to interpret, given the low numbers of events and lemborexant's mechanism of action. Serious falls are a particular concern; however, they are not uncommon in an older adult patient population, and there were only two in the lemborexant groups, making interpretation difficult.

Special reviews of falls and fractures are presented in Section 8.2.5.

Clinical Reviewer Comments*: Although the frequency of serious adverse events in phase 3 studies was higher in the lemborexant treatment arms than placebo, the total exposure was also greater with the lemborexant arms. Assessment of the incidence of serious adverse events per 100 patient-years shows that the risk differences between the treatment arms are relatively low and does not provide clear support for specific lemborexant safety concerns. Most of the AEs of interest prespecified by the Applicant (e.g., cataplexy, seizure, sleep paralysis, somnolence) were not categorized as serious adverse events and will be discussed in Section 8.2.4. The potential signal for falls or fractures is also discussed in Section 8.2.5, and there was no clear evidence for a study drug effect on these events.*

Serious adverse events and other studies: The Applicant reports that there were no treatment emergent serious adverse events in Study 102 (respiratory safety study), Study 104 (hepatic safety study), Study 105 (renal safety study), Study 202 Core (Alzheimer's disease related study), or in studies of healthy subjects.

Notably, in the phase 2 and 3 database, there were three serious adverse events that could be related to thrombosis: 1 acute myocardial infarction (LEM10), 1 deep vein thrombosis (LEM10), and 1 ischemic stroke (LEM2.5) compared to none on placebo (Source: 120-day safety update, table 12, Study 303 CSR Table 27, Study 202 CSR). The narratives of these cases were reviewed:

- In the extension phase of Study 202, an 80-year old African American male in the LEM2.5 group (subject E2006-G000-202-(b) (6) presented with symptoms that were deemed related to an ischemic stroke on day 47, which led to premature study termination. This subject had a medical history of hypertension, hyperlipidemia, diabetes type II, vascular disease s/p angiopathy, and stroke. Given the subject's age and medical history with multiple risk factors for cerebrovascular accident (including a prior stroke), it is difficult to attribute the ischemic stroke to lemborexant treatment.

- In Study 303, deep vein thrombosis was reported on day 188 in subject E2006-G000-303-(b) (6) This subject was a 46 year old African American woman with a history of uterine leiomyoma, hypertension, and polycystic ovaries. She was receiving concomitant medications including hydralazine, levonorgesterel IUD, and lisinopril. On Day 114 of treatment with lemborexant 10 mg, she developed severe leg pain and was found to have a deep vein thrombosis. She received treatment for the thrombosis

including enoxaparin and rivaroxaban and on Day 179 the event of deep vein thrombosis was considered resolved.

- In Study 303, acute myocardial infarction was reported on day 291 in subject E2006-G000-303-(b) (6) This subject t was a 66-year-old white male with a history of myocardial ischemia, obesity, chronic bronchitis, chronic hepatitis, hypercholesterolemia, and hypertension. On Day 111 of treatment with lemborexant 10 mg , he experienced chest pain and was diagnosed with acute myocardial infarction. The patient received a stent and pharmacological treatment; study drug was temporarily stopped. The symptoms resolved and the patient resumed treatment with lemborexant 10 mg and completed the study. This patient had several risk factors for myocardial infarction (including myocardial ischemia), and it is difficult to attribute the event to lemborexant treatment.

The database for phase 2 and 3 was reviewed there were no additional on-drug incidents of acute myocardial infarction, deep vein thrombosis, or ischemic stroke. Although there were three occurrence of adverse events consistent with thrombosis in subjects receiving lemborexant as compared to none for placebo, the overall exposure was higher for lemborexant compared to placebo in the development program. Two out of the three subjects described above had multiple significant predisposing factors and it is difficult to attribute the events to lemborexant treatment. We were unable to find support in the literature linking orexin receptor antagonist therapy with thrombus formation. Therefore, we do not believe there was a clear signal for increased thrombotic-related events associated with lemborexant.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

First 30 days: According to the Applicant, the frequencies of discontinuation during the first 30 days of Study 303 and 304 were 1.4% and 2.6% for lemborexant 5 and 10 mg, respectively, and 1.5% in the placebo group. The most common adverse reactions leading to discontinuation of lemborexant in the first 30 days were somnolence (0.7% for 5 mg, 1.0% for 10 mg, and 0.4% for placebo) and nightmares (0.3% for 5 mg, 0.3% for 10 mg, and 0% for placebo).

Longer term: The frequencies of discontinuation due to treatment-emergent adverse events (TEAEs) in the 6-month placebo-controlled period of Study 303 were 4.1% for LEM5 and 8.3% for LEM10, compared to 3.8% in the placebo group. The most common reasons for discontinuation and occurring in more than one subject within a treatment arm were somnolence (1.0% for 5 mg, 2.9% for 10 mg, and 0.6% for placebo), nightmares (0.3% for 5 mg, 1.3% for 10 mg, and 0% for placebo), and palpitations (0% for 5 mg, 0.6% for 10 mg, and 0% for placebo).

Considering the full Phase 3 Pool, which includes 12-months exposure, the discontinuation due to any TEAE was 4.9% for lemborexant compared to placebo (2.7%). Discontinuation rates due to TEAE were higher for LEM10 (6.2%) than LEM5 (3.5%).

Table 68 presents TEAEs leading to discontinuation in 2 or more subjects treated with lemborexant in the Phase 3 Pool. The most common were somnolence (1.7% of all subjects), and nightmares (0.5% of all subjects).

Table 68: TEAE Leading to Discontinuation From Study Drug Within 14 Days of Last Dose by Increasing Frequency, Phase 3 Pool

MedDRA Preferred Terms	Lemborexant 5 mg (N=713) n (%)	Lemborexant 10 mg (N=705) n (%)	Lemborexant LEM5+LEM10 (N=1418) n (%)	Placebo (N=528) n (%)
Any TEAE leading to discontinuation due to study drug	25 (3.5)	44 (6.2)	69 (4.9)	14 (2.7)
Palpitations	0	2 (0.3)	2 (0.1)	0
Fatigue	1 (0.1)	1 (0.1)	2 (0.1)	0
Lethargy	1 (0.1)	1 (0.1)	2 (0.1)	0
Abnormal Dreams	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.2)
Fall	1 (0.1)	2 (0.3)	3 (0.2)	0
Dizziness	3 (0.4)	2 (0.3)	5 (0.3)	1 (0.2)
Headache	4 (0.6)	1 (0.1)	5 (0.3)	2 (0.4)
Nightmare	3 (0.4)	4 (0.6)	7 (0.5)	0
Somnolence	8 (1.1)	16 (2.3)	24 (1.7)	3 (0.6)

Source: Clinical Reviewer created table using data from the 120-Day ISS, Table 21

Clinical Reviewer Comments*: The discontinuation rates attributed to a TEAE were higher for lemborexant compared to placebo: LEM10 (6.2%), LEM5 (3.5%), placebo (2.7%).*

Falls, an important adverse event for a sleep drug, were uncommon as a reason for discontinuation (0.2% of subjects).

8.2.4.4. Significant Adverse Events

The Applicant considered significant adverse events to be due to treatment emergent laboratory abnormalities, exposure during pregnancy or breastfeeding, or overdose or misuse:

Treatment emergent laboratory abnormalities: Laboratory abnormalities are reviewed in Section 8.2.4.6. No clinically meaningful laboratory abnormalities were found with lemborexant.

Pregnancy or exposure to breastfeeding: One pregnancy was reported in a 22 year-old subject (Subject (b) (6) who received LEM10 during Study 012 (famotidine treatment group). The subject had a negative pregnancy test the day before receiving single doses of famotidine 40 mg and LEM10. Ten days later, the subject had positive urine and serum pregnancy tests and elected to terminate the pregnancy.

Drug Misuse: The Applicant reports there was no evidence for abuse or diversion of study medication. Review of the abuse liability data concurs with the Applicant's conclusions, see Section 8.2.5.9 for review.

Overdose: The Applicant reports there were 4 intentional overdoses and 2 accidental overdoses. The maximum overdose of lemborexant was 10 mg per day. No AEs were reported associated with these events.

Both accidental overdoses were in Study 304. The first accidental overdose was in the zolpidem ER 6.25 mg arm, Subject (b) (6) 77-year-old white female. On study day 20, the patient reported dizziness and confusional state after overdose, classified as mild in severity. The subject recovered from the event on the same day. The second accidental overdose was Subject (b) (6) 69-year-old, white, female in the LEM10 arm. The event occurred on study day 27 and was classified as mild with resolution the same day.

Table 69 provides narrative details on the subjects with intentional overdoses. None of the intentional overdoses were associated with suicidality or self-injurious behavior, and no TEAEs were reported associated with these events.

Table 69: Summary of Subjects with Intentional Overdose in All Studies

Subject Study Treatment	**Demographics**	**Details**
Subject (b) (6) Study E2006-G000-303 Placebo	63 year-old African American male	Subject was accidentally enrolled twice and was taking the study drug (placebo) twice nightly. He was discontinued from the study when the issue was discovered.
Subject (b) (6) Study E2006-G000-303 LEM5	41 year-old Asian female	On study day 89, the subject had difficulty sleeping and took 2 study drug tablets. No action was taken and no AEs were reported.
Subject (b) (6) Study E2006-G000-303 LEM5	37-year-old African American female	On study day 34, the subject began taking a second dose of study drug when the first dose was not effective. She was unsure how often she did this. She denied associated adverse events. She was lost to follow-up on Day 60.
Subject (b) (6) Study E2006-G000-303 LEM5	20-year-old African American female	On study days 185, 186, 192, 193, 220, 221, 255, the subject took an additional tablet when the first one didn't work. No treatments or adverse events were reported.

Source: Clinical Reviewer generated table from associated subject narratives

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions of All Severities

The tables below show treatment emergent adverse events using different pooling strategies.

In light of the disparate durations of the phase 3 studies (303 and 304), simple pooling of the adverse events from both studies would not be interpretable. To avoid this issue, the clinical reviewer performed an adverse event analysis for Studies 303 and 304 that was restricted to the first 30 days (Table 70), including the recoding strategy described in Section 8.2.1. The findings for zolpidem and the relative risk (RR) are also shown (all lemborexant vs. placebo). The findings for infection are considered spurious. There appears to be a dose effect for somnolence and nightmares/abnormal dreams; the incidence of nightmares/abnormal dreams is identical for placebo for LEM5.

Table 70: Adverse Events ≥2% and Greater Than Placebo, First 30 Days Combined Studies 303 and 304

	Lemborexant			Placebo	Zolpidem	RR
MedDRA Preferred Terms	5 mg N=580	10 mg N=582	All N=1162	N=528	N=263	
Somnolence,Fatigue, and related terms[a]	40 (6.9%)	56 (9.6%)	96 (8.3%)	7 (1.3%)	9 (3.4%)	6.2
Somnolence only	30 (5.2%)	49 (8.4%)	79 (6.8%)	7(1.3%)	5 (1.9%)	5.1
Any Infection[b]	40 (6.9%)	27 (4.6%)	67 (5.8%)	24 (4.5%)	8 (3%)	1.3
Headache	34 (5.9%)	26 (4.5%)	60 (5.2%)	18 (3.4%)	13 (4.9%)	1.5
Nightmare or Abnormal dreams	5 (0.9%)	13 (2.2%)	18 (1.5%)	5 (0.9%)	0	1.6

Abbreviations: RR, relative risk (lemborexant (5 mg + 10 mg) vs. placebo)
Source: Clinical Reviewer generated table from recoded safety database for the first 30-days of studies 303 and 304; includes recoded preferred terms.
a. Includes MedDRA preferred terms: fatigue, lethargy, sedation, sluggishness, somnolence, corresponding to the current FDA Broad Somnolence classification
b. Includes URI, cold, rhinitis, upper resp tract infection, flu-like illness

Whereas Table 70 considered only the adverse events that occurred in the first 30 days of Studies 303 and 304, the reviewer performed an alternative analysis that considered all of the adverse events in these studies. To take the differing durations of exposure into account, however, the adverse events were expressed in terms of time of exposure, i.e., events per 100 patient-years (Table 71). Similar adverse events are pooled, and only preferred term groupings where the risk difference exceeds 2 events per 100 patient-years are tabulated (right column).

Table 71: Adverse Events per 100 Patient-years: Study 303, Treatment Periods 1 and 2 (6 Months Each) and Study 304 (30 days); Risk Difference > 2 per 100 Patient-years

	Lemborexant			Placebo	Zolpidem 6.25 mg	Risk Difference
	5 mg	10 mg	Both			
Exposure (patient-years)	**340.2**	**315.2**	**655.3**	**158.6**	**21.0**	
Somnolence, fatigue, sedation	66 (19.4)	99 (31.4)	165 (25.2)	10 (6.3)	10 (47.5)	18.9
Fatigue, lethargy, malaise, asthenia, sluggishness	20 (5.9)	22 (7)	42 (6.4)	1 (0.6)	4 (19)	5.8
Parasomnia*	11 (3.2)	17 (5.4)	28 (4.3)	(0)	(0)	4.3
Nausea, vomiting, dyspepsia, gastritis	28 (8.2)	23 (7.3)	51 (7.8)	8 (5)	7 (33.3)	2.7
Arrhythmia*	11 (3.2)	10 (3.2)	21 (3.2)	1 (0.6)	2 (9.5)	2.6

***Parasomnia** includes sleep paralysis, hypnagogic hallucination, hypnopompic hallucination, exploding head syndrome, parasomnia, somnambulism
***Arrhythmia** includes ventricular extrasystoles, atrial fibrillation, arrhythmia, extrasystoles, tachycardia, arrhythmia supraventricular, nodal arrhythmia, sinus bradycardia, supraventricular extrasystoles
Risk difference represents lemborexant (both) minus placebo.
Source: Analyses from 120-day Safety Update: \\0012\m5\datasets\iss-phase-2-3\analysis\adam\datasets\adae.xpt and adsl.xp

There is an obvious signal for somnolence, fatigue, and sedation that is dose-related, with a risk difference (all lemborexant vs. placebo) of 18.9 events per 100 patient-years. Parasomnias were also dose-related, at a rate of 4.3 events per 100 patient-years, compared to none in the placebo group. Please refer to Section 8.2.5.5 for further discussion about parasomnias.

Nausea, vomiting and arrhythmias are more difficult to interpret; the disparities were not large, there were no dose-response, and there are no known underlying mechanisms. These adverse events are not clearly drug-related.

8.2.4.6. Laboratory Findings

Overview: The Applicant submitted data and presented analyses regarding hepatobiliary chemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], total bilirubin [tBili]), renal chemistry parameters (blood urea nitrogen, creatinine), electrolytes, hematology parameters (red blood cells, hematocrit, hemoglobin, white blood cells with differentials, platelets), and urinalysis parameters. The Applicant concluded that there were no clinically meaningful laboratory findings (mean changes or shifts) for LEM5 or LEM10 compared to placebo, based on pooled analyses from Baseline to Month 1 in the phase 3 pool as well as the all insomnia pool. The Applicant also concluded that there were no clinically important changes in laboratory findings associated with long-term exposure, based on evaluation of Study 303 up to 12 months. Finally, the Applicant reported that that there were no clinically meaningful mean changes or shifts from baseline for laboratory parameters in subjects participating in the special safety Studies 104 (renal impairment) and 105 (hepatic impairment).

To further explore for potential safety signals, the clinical review team conducted independent analyses of the Applicant-submitted safety data as described below.

Chemistry:
Evaluation for potential effects of lemborexant on chemistry parameters was performed by the clinical review team by assessing mean changes from baseline, significant outlier cases, and the incidence of shifts from normal to abnormal values by treatment group. These analyses focused primarily on data from the 6-month placebo-controlled phase of Study 303 and from Study 304. Studies 303 and 304 were analyzed separately because of the significant difference in exposure duration between the studies (6 months vs. 30 days) which could affect interpretation of the results when pooled. Other studies were considered less useful in this review of potential effects of lemborexant on chemistry parameters because they had shorter durations of exposure and/or lacked a placebo comparator. However, the Applicant's presentation of the results from the other studies were reviewed to assess potential signals not identified from analyses of Studies 303 and 304.

Mean Changes
In Study 303, there were no meaningful differences by treatment arm in mean changes from baseline at Month 1, Month 2, Month 3, or Month 6 for bicarbonate, chloride, potassium, sodium, ALT, AST, ALP, direct bilirubin (dBili), tBili, blood urea nitrogen (BUN), creatinine, albumin, calcium, total cholesterol, globulin, glucose, iron, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, or urate (data not shown). In Study 304, there were similarly no meaningful differences by treatment arm in mean changes from baseline to Day 30/31 for the same chemistry parameters (data not shown).

Outliers
Refer to Table 72 and Table 73 for presentations of the incidences of markedly abnormal chemistry parameter values that were reported during Studies 303 and 304, respectively. For both tables, chemistry parameters in which the incidence of markedly abnormal values with LEM5 or LEM10 was not greater than placebo are not presented.

Table 72: Study 303 - Incidence of Markedly Abnormal Chemistry Laboratory Parameters

Laboratory Test / Threshold	Placebo (N=319) n (%)	LEM5 (N=314) n (%)	LEM10 (N=314) n (%)
ALT >3x ULN	2 (0.6)	1 (0.3)	3 (1.0)
AST >3x ULN	2 (0.6)	0	3 (1.0)
Calcium ≤7 mg/dL	0	1 (0.3)	0
Cholesterol >300 mg/dL	2 (0.6)	8 (2.5)	7 (2.2)
Creatinine >1.5 ULN	0	0	3 (1.0)
GGT >3x ULN	1 (0.5)	5 (1.6)	2 (0.6)
Glucose >160 mg/dL	5 (1.6)	10 (3.2)	5 (1.6)
Potassium >5.5 mmol/L	4 (1.3)	2 (0.6)	6 (1.9)
Sodium <130 mmol/L	0	1 (0.3)	1 (0.3)
Sodium >150 mmol/L	1 (0.3)	0	2 (0.6)
Triglycerides >300 mg/dL	15 (4.7)	15 (4.8)	25 (8.0)

Source: Reviewer-created from data from Study 303 Clinical Study Report, Table 14.3.4.4.1.
ULN = upper limit of normal. The occurrence of treatment-emergent markedly abnormal laboratory values is defined as a subject having any postbaseline laboratory value with a change from baseline to the specified threshold.

Table 73: Study 304 - Incidence of Markedly Abnormal Chemistry Laboratory Parameters

Laboratory Test / Threshold	Placebo (N=209) n (%)	LEM5 (N=266) n (%)	LEM10 (N=268) n (%)
Cholesterol >300 mg/dL	1 (0.5)	6 (2.3)	3 (1.1)
GGT >3x ULN	1 (0.5)	5 (1.9)	2 (0.7)
Glucose >160 mg/dL	2 (1.0)	3 (1.1)	3 (1.1)
tBili >1.5x ULN	0	2 (0.8)	1 (0.4)

Source: Reviewer-created from data from Study 304 Clinical Study Report, Table 14.3.4.4.1.
ULN = upper limit of normal. The occurrence of treatment-emergent markedly abnormal laboratory values is defined as a subject having any post-baseline laboratory value with a change from baseline to the specified threshold.

Hy's Law Analyses

ALT, AST, tBili, and ALP data from Studies 303 and 304 were analyzed to assess whether any subjects in the studies met Hy's Law laboratory criteria, which may indicate significant drug-induced liver injury. The specific analyses identified cases in which subjects met any of the following criteria at the same visit, as well as cases in which subjects met the criteria for individual parameters at any time during the studies:

- ALT or AST ≥ 3x ULN, tBili ≥ 1.5x ULN and ALP normal
- ALT or AST ≥ 3x ULN, tBili ≥ 2x ULN and ALP normal
- ALT or AST ≥ 5x ULN, tBili ≥ 3x ULN and ALP normal
- ALT or AST ≥ 3x ULN, tBili ≥ 1.5x ULN and ALP > normal
- ALT or AST ≥ 3x ULN, tBili ≥ 2x ULN and ALP > normal
- ALT or AST ≥ 5x ULN, tBili ≥ 3x ULN and ALP > normal

Study 303: One subject receiving placebo (303-[redacted] (b) (6) met the criteria of ALT or AST ≥3x ULN, tBili ≥1.5x ULN, and ALP normal at the same visit. No subjects receiving lemborexant met

any of the above criteria at the same visit or at any time during the study. The analysis of possible Hy's Law cases for Study 303 included the 6-month extension phase in addition to the initial 6-month placebo-controlled phase, such that there was a cohort of subjects who received lemborexant 5 mg or 10 mg for 12 months.

Study 304: No subjects in the study met any of the above criteria at the same visit or at any time during the study.

Shifts
For both Studies 303 and 304, JMPClinical was used to conduct laboratory shift analyses. In these analyses, the incidence of shifts in laboratory value magnitude category (e.g., from <2x ULN to 2-5x ULN) from baseline to the maximum value for the patient during the trials were compared across treatment arms. The Applicant's tabulations of shifts from baseline to follow-up visits were also reviewed. There were no meaningful patterns of shifts for most of the chemistry parameters; analyses for select parameters of potential clinical relevance are described below.

Shift tables for Studies 303 and 304 for ALT and AST are presented in Table 74 and Table 75, respectively. In Study 303, there was a small dose-dependent increase in the proportion of subjects receiving lemborexant who had post-baseline maximum ALT values ≥2x the ULN. This pattern was not evident for ALT in Study 304, and there was no clear pattern of AST shifts in either study.

Table 74: ALT Shift Tables, Studies 303 and 304

STUDY 303

	Placebo (N=319)		**LEM5 (N=314)**		**LEM10 (N=314)**	
ALT Baseline:	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN
ALT Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALT < 2x ULN	1 (0.3)	0	298 (94.9)	2 (0.64)	284 (90.5)	1 (0.3)
2x ≤ ALT < 5x ULN	2 (0.6)	0	5 (1.59)	0	10 (3.2)	1 (0.3)
5x ≤ ALT < 10x ULN	0	0	1 (0.32)	0		1 (0.3)

STUDY 304

	Placebo (N=209)		**LEM5 (N=266)**		**LEM10 (N=268)**	
ALT Baseline:	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN
ALT Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALT < 2x ULN	201 (96.2)	1 (0.5)	262 (98.5)	1 (0.4)	262 (97.8)	1 (0.4)
2x ≤ ALT < 5x ULN	2 (1.0)	0	3 (1.1)	0	2 (0.8)	0
5x ≤ ALT < 10x ULN	0	0	0	0	0	0

Table 75: AST Shift Tables, Studies 303 and 304

STUDY 303

	Placebo (N=319)	**LEM5 (N=314)**	**LEM10 (N=314)**

AST Baseline:	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN
AST Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AST < 2x ULN	301 (94.4)	0	305 (97.1)	0	292 (93.0)	0
2x ≤ AST < 5x ULN	2 (0.6)	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)
5x ≤ AST < 10x ULN	0	0	0	0	1 (0.3)	0

STUDY 304

	Placebo (N=209)		LEM5 (N=266)		LEM10 (N=268)	
AST Baseline:	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN	<2x ULN	≥ 2x ULN
AST Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AST < 2x ULN	202 (96.7)	1 (0.5)	264 (99.3)	1 (0.4)	264 (98.5)	0
2x ≤ AST < 5x ULN	1 (0.5)	0	1 (0.4)	0	1 (0.4)	0
5x ≤ AST < 10x ULN	0	0	0	0	0	0

Source: Reviewer created based on analyses of Study 303 (placebo-controlled 6-month period) and Study 304 laboratory value data in JMPClinical.

Shift tables for total cholesterol and triglycerides in Study 303 are presented in Table 76 below. Laboratory tests for HDL and LDL, which may have been helpful for characterizing potential effects on lipids, were not performed in Study 303. Although there was no evidence for a dose-response (i.e., shifts with lemborexant 5 mg were similar to those with placebo), a greater proportion of patients receiving lemborexant 10 mg experienced shifts from normal cholesterol and triglyceride values at baseline to greater than normal values during post-baseline assessments.

Table 76: Total Cholesterol and Triglyceride Shift Tables, Study 303

TOTAL CHOLESTEROL

	Placebo (N=319)		LEM5 (N=314)		LEM10 (N=314)	
Cholesterol Baseline:	≤ULN	>ULN	≤ULN	>ULN	≤ULN	>ULN
Cholesterol Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ULN	134 (42.0)	29 (9.1)	131 (41.7)	32 (10.2)	119 (37.9)	26 (8.3)
>ULN	34 (10.7)	119 (37.3)	30 (9.6)	120 (38.2)	38 (12.1)	127 (40.4)

TRIGLYCERIDES

	Placebo (N=319)		LEM5 (N=314)		LEM10 (N=314)	
Triglyceride Baseline:	≤ULN	>ULN	≤ULN	>ULN	≤ULN	>ULN
Triglycerides Maximum	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ULN	230 (72.1)	29 (9.1)	238 (75.8)	22 (7.0)	233 (74.2)	19 (6.1)
>ULN	17 (5.3)	40 (12.6)	17 (5.4%)	36 (11.5)	26 (8.3)	32 (10.2)

Source: Reviewer-created; adapted from the Applicant's Study 303 CSR (Table 14.3.4.2.1.2). Data is from baseline to end of treatment during the 6-month placebo-controlled period.

Serious Adverse Events and Discontinuation Involving Changes in Chemistry Parameters
The narratives of subjects who experienced treatment-emergent serious adverse events or discontinuations involving changes in chemistry parameters were reviewed to help characterize the potential clinical significance of changes in laboratory parameters.

In the all subjects with insomnia pool (Studies 001 Part B, 107, 201, 303, 303-EXT, and 304), there were no subjects who experienced treatment-emergent serious adverse events that included preferred terms coded within the SOC of Investigations (Source: Applicant-submitted ISS, Table 4.2.4.3). There were four treatment-emergent adverse events leading to discontinuation within the Investigations SOC which described changes in chemistry parameters. Of these four cases, three occurred in subjects receiving zolpidem ER (N=263 total subjects in the pool), and one case of GGT increased occurred in a subject receiving lemborexant 10 mg (of N=815 total LEM10 subjects in the pool).

> Subject 304-(b) (6) was a 57-year old woman with a past medical history of GGT increased. During screening, she was found to have a GGT of 244 U/L (normal range 5 – 24 U/L). Laboratory studies collected on Study Day 1 (prior to initiating treatment with lemborexant 10 mg) found that her GGT was 263 U/L. She was discontinued from the study after 6 days of receiving lemborexant due to the event of increased GGT.

This case does not support a causal relationship between lemborexant and increased GGT, because the value that triggered the discontinuation was obtained on Study Day 1.

Reviewer's Summary and Conclusions for Laboratory Findings:
The Applicant concluded, based on their analyses, that there were no clinically meaningful effects of lemborexant on clinical laboratory or hematological parameters over time. The clinical reviewer is in general agreement with the Applicant's conclusions based on the review of laboratory data as described above.

Lemborexant was not associated with any clinically meaningful changes in mean chemistry or hematology laboratory values as compared to placebo. Hy's Law analyses did not identify any cases of lemborexant-associated drug-induced liver injury. There were a small number of outliers who experienced markedly abnormal chemistry parameters during the course of Studies 303 and 304. Of the outliers, the strongest potential signal was the proportion of patients in Study 303 who had a triglyceride measurement >300 mg/dL during the study (n=25 (8.0%) for LEM10 vs. n=15 (4.7) for placebo). Shift table analyses for Study 303 supported a possible association between lemborexant 10 mg treatment and an increase in total cholesterol and triglycerides. However, in light of the numerous laboratory measurements assessed, the lack of a dose-response for this effect, and the relatively small differences in shift percentages between LEM10 and placebo groups, these could well be chance findings, and we conclude that the findings do not merit communication in labeling.

That being said, there may be some biological plausibility for an effect of orexin receptor antagonism on metabolic parameters, given the role of the orexin system in modulating food intake and energy balance [30]. In a mouse model of type 2 diabetes (db/db), the orexin receptor antagonist suvorexant was reported to improve glucose tolerance by reducing gluconeogenic factors [31]. In contrast with the mouse findings, a recently published observational study in diabetic (n=45) and non-diabetic (n=43) humans reported that nine months of treatment with the orexin receptor antagonist suvorexant was associated with significantly decreased HDL in diabetic patients and significantly increased hemoglobin A1C and LDL in non-diabetic patients. Taken together, it is plausible that orexin receptor antagonism affects metabolic parameters, but the evidence from the literature and the lemborexant development program seems inconclusive.

8.2.4.7. Vital Signs

Overview: The Applicant reports that there were no clinically meaningful effects of lemborexant on vital signs over time, as evidenced by pooled data analyses as well as exposure duration-based analyses through Month 12, and there were no dose-related trends. When comparing the Month 1 data to Month 12 (end of treatment), there were no clinically important mean values or mean changes from Baseline by duration of exposure for any vital signs parameter, with the exception of minor weight loss (Source: 120-Day Update, Table 6.1.5.1.). The Applicant reported that incidence of markedly abnormal vital signs was low and similar across placebo, LEM5, and LEM10 groups and in all data pools (e.g., phase 3 pools, all subjects with sleep disorders, subjects with sleep disorders other than insomnia).

The clinical review team reviewed the submitted vital sign data according to: 1) mean change from baseline to end-of-treatment, by treatment group; 2) the frequency of subjects shifting from normal to abnormal during the study (using Applicant's prespecified definitions for "abnormal"); and 3) analysis of outliers (data not shown, because there were no pertinent findings to present). We agree with the Applicant's assertion that there were no dose-related trends suggestive of a drug-associated signal.

See Table 77 for the number of subjects with abnormal values in vital signs in the Phase 3 Pool (studies 303 and 304).

Table 77: Abnormal Vital Signs, Phase 3 Pool

Parameter (Unit)	Placebo (N=528) n (%)	Zolpidem ER 6.25 mg (N=263) n (%)	Lemborexant 5 mg (N=713) n (%)	Lemborexant 10 mg (N=705) n (%)	Lemborexant Total (N=1418) n (%)
Systolic Blood Pressure (mmHg)					
n [a]	523	256	711	698	1409
Notable Low (<90 and decrease >=20)	0	1 (0.4)	0	0	0
Notable High (>180 and increase >=20)	1 (0.2)	0	1 (0.1)	2 (0.3)	3 (0.2)
Diastolic Blood Pressure (mmHg)					
n [a]	523	256	711	698	1409
Notable Low (<50 and decrease >=15)	1 (0.2)	0	2 (0.3)	0	2 (0.1)
Notable High (>105 and increase >=15)	1 (0.2)	0	2 (0.3)	1 (0.1)	3 (0.2)
Pulse Rate (beats/min)					
n [a]	522	256	711	697	1408
Notable Low (<50 and decrease >=15)	1 (0.2)	2 (0.8)	4 (0.6)	2 (0.3)	6 (0.4)
Notable High (>120 and increase >15)	0	0	0	1 (0.1)	1 (0.1)
Respiratory Rate (breaths/min)					
n [a]	519	255	702	685	1387
Notable Low (<8 and decrease >=4)	0	0	2 (0.3)	2 (0.3)	4 (0.3)
Notable High (>30 and increase >=10)	0	0	0	0	0
Weight (kg)					
n [a]	523	256	711	698	1409
Notable Low (decrease of >=7%)	8 (1.5)	2 (0.8)	20 (2.8)	16 (2.3)	36 (2.6)
Notable High (increase of >=7%)	15 (2.9)	1 (0.4)	24 (3.4)	37 (5.3)	61 (4.3)

Abbreviation: ER, extended release
Source: Applicant ISS 120-Day Update, Table 6.1.5.2.

Pulse Rate: Review of Applicant-submitted data from the phase 3 pool found no clinically meaningful mean changes from baseline to EOT in pulse rate for placebo (-1.1), LEM5 (-2.7), and LEM10 (-2.3). In addition, there were no dose-related trends suggestive of a signal. Notably high or low values for pulse occurred in a small percentage of subjects, as described in Table 77, and there were no clear differences between the groups. (Source, Applicant ISS 120-Day Update, Table 6.1.5.1.)

Blood Pressure: In the phase 3 pool, there were no clinically meaningful changes over time in systolic or diastolic blood pressure. Systolic change from Baseline to EOT remained similar across groups: placebo (0.3), LEM5 (-1.2), and LEM10 (-0.4); and diastolic change from Baseline to EOT remained similar across groups: placebo (0.1), LEM5 (-0.3), and LEM10 (0.7). There were no dose-related trends. (Source, Applicant ISS 120-Day Update, Table 6.1.5.1.)

Temperature: There were no clinically meaningful changes over time (EOT) for temperature, with mean changes in temperature (Celsius) of -0.07 (placebo), -0.04 (LEM5), and -0.03 (LEM10; Table 6.1.5.1). There were no dose-related trends (Source, Applicant ISS 120-Day Update, Table 6.1.5.1.).

Respiratory Rate: There were no clinically meaningful changes over time (EOT) for respiratory rate (Source, Applicant ISS 120-Day Update, Table 6.1.5.1).

Weight: In the phase 3 pool, which included data up to 12 months, relatively small percentages of subjects experienced increases or decreases in weight ≥7% in the placebo, LEM5, and LEM10 groups. The mean changes in weight (kg) were 0.14 (placebo), 0.21 (LEM5), and 0.30 (LEM10). As described in Table 77 above, there were decreases of ≥7% in 1.5% of placebo subjects, 2.8% of LEM5 subjects, and 2.3% of LEM10 subjects, and increases of ≥7% of 2.9% of placebo subjects, 3.4% of LEM5 subjects, and 5.3% of LEM10 subjects (Source, Applicant ISS 120-Day Update, Table 6.1.5.1).

Data for the mean changes in weight for Study 303 (6-month placebo controlled) suggest that there were no significant differences between lemborexant and placebo (Source, Study 303 CSR, Table 14.3.4.5.1.1). The mean change in weight from Baseline to Month 6 in kilograms (SD) was 0.44 (2.8) for placebo, 0.64 (2.4) for LEM5, and 0.61 (2.8) for LEM10. Maximum increases in weight from baseline to month six were similar across groups (10, 9.9, and 11.5 for placebo, LEM5, and LEM10, respectively). Maximum weight loss was higher for placebo compared to lemborexant (-21.6, -13, and -12.4 for placebo, LEM5, and LEM10, respectively).

Clinical Reviewer Comments*: There were no clinically meaningful differences between LEM5 or LEM10 compared to placebo on vital signs (pulse rate, blood pressure, temperature, respiratory rate, or weight).*

8.2.4.8. Electrocardiograms (ECGs)

The Applicant conducted nonclinical and human clinical studies to assess cardiac safety.

As summarized by the QT Interdisciplinary Review Team (QT-IRT) reviewers, effects of oral doses of lemborexant administered during the daytime on blood pressure, heart rate, and ECG parameters were examined in 4 conscious telemetered male cynomolgus monkeys at 10, 30, and 100 mg/kg, which was considered the definitive nonclinical study to assess these parameters. Lemborexant did not affect blood pressure, heart rate, PR interval, or QRS duration at doses up to 100 mg/kg.

In healthy subjects taking single doses of lemborexant (single dose pool), twelve-lead ECGs were recorded predose and at various times post-dose (30 min, 1, 2, 4, 6, 8, 9, 12, 24 hours, 2 to 7 days, and 8 to 27 days), and from Baseline to end-of-study. Mean Baseline values were within normal ranges for all ECG parameters, and there were no clinically meaningful changes over time for mean values in the PBO, LEM5, LEM10, and other groups. There were no shifts from Baseline of clinical concern, and the pattern of shifts was similar across the treatment arms.

In the Phase 3 Pool, ECG parameters (heart rate, QRS duration, PR, QT, QTcF, and RR intervals) were analyzed at Baseline, Month 1, and Month 12. Mean Baseline values were within normal

ranges for these ECG parameters. As detailed in Table 78 below, there were no clinically meaningful changes over time for mean values in the PBO, LEM5 and LEM10 groups, no dose related trends, and no clinically meaningful shifts from baseline. Moreover, the pattern of shifts was similar across the groups.

Table 78: Abnormal QTc, PR, and QRS Results, Phase 3 Pool (Studies 303 and 304)

ECG Category	Placebo (N=528) n (%)	5 mg (N=713) n (%)	10 mg (N=705) n (%)
QTc*			
Subjects with baseline and postbaseline data	519	709	696
At least one postbaseline increase of >30 msec	37 (7.1)	61 (8.6)	55 (7.9)
At least one postbaseline increase of >60 msec	1 (0.2)	1 (0.1)	1 (0.1)
At least one postbaseline value of >450 msec	22 (4.2)	30 (4.2)	41 (5.9)
At least one postbaseline value of >500 msec	0	0	1 (0.1)
PR Interval			
Subjects with baseline and postbaseline data	518	706	692
At least one postbaseline value of >220 msec	15 (2.9)	20 (2.8)	30 (4.3)
QRS Interval			
Subjects with baseline and postbaseline data	519	709	696
At least one postbaseline value of >120 msec	17 (3.3)	15 (2.1)	12 (1.7)

*QTc = QT interval corrected for Fridericia's formula
Source: Modified from Applicant's 120-Day Safety Update, Table 23

8.2.4.9. QT

During the lemborexant development program, the Applicant inquired whether they had sufficient data from two phase 1 studies (002 and 003) to characterize the proarrhythmic risk of lemborexant according to exposure-response analyses as opposed to a single thorough QT study. The QT-IRT found this proposal to be acceptable.

The QT-IRT team reviewed the concentration-QTc relationship and confirmed that the upper bound of the 2-sided 90% CI for the predicted mean ΔΔQTcF at the supratherapeutic exposures (50-mg dose) was < 10 milliseconds (ms). Drug interaction studies with CYP3A4 inhibitors (itraconazole and fluconazole) indicate increased exposure of lemborexant (C_{max} by ~1.6-fold). The QT-IRT team determined that the supratherapeutic exposures (50-mg dose) provided an adequate margin for the characterization of the exposure-response relationship. The QT-IRT team concluded that lemborexant does not prolong the QT interval to any clinically relevant extent at a dose 5 times the maximum recommended dose of LEM10.

In addition to the exposure-response analyses, the clinical reviewer assessed data submitted by the Applicant on shifts from baseline in QTcF. In healthy subjects, there were no shifts from baseline of clinical concern noted in the single dose or multiple-dose pools, and the pattern of shifts were similar across treatment arms. There were no notable differences in the incidence of abnormal QTcF results between the placebo and LEM5, LEM10, and other groups.

In the Phase 3 Pool, there were no clinically meaningful changes over time for mean values in the placebo, LEM5, LEM10, and other groups. For the limited number of patients who experienced shifts of potential clinical concern, the incidence was similar across treatment arms.

In the study with the longest exposure to lemborexant (Study 303/303-Ext), there were no subjects in any treatment arm with a single reported post-baseline QTcF > 500 msec (Study 303 CSR, Table 14.3.4.6.3.2).

Clinical Reviewer Comments*: Lemborexant does not appear to have a clinically meaningful effect on ECG parameters, including QT prolongation.*

8.2.4.10. Immunogenicity

There was no dedicated immunogenicity study conducted as part of the drug development program. In the Phase 3 Pool, there were no reports of discontinuation due to adverse events within the SOC immune system disorders, including hypersensitivity. The clinical reviewer searched the phase 2 and 3 database for MedDRA terms associated with rash, allergy/allergic, or hypersensitivity with the following results: 2 cases in LEM15/25, 4 cases for LEM10, zero for LEM5, and two cases in the placebo groups. Table 79 lists all MedDRA preferred terms and verbatim terms of “rash,” “allergy,” “allergic,” or “hypersensitivity” in the phase 2 and 3 database.

There was no apparent relationship to duration on study drug. None of the events associated with hypersensitivity reactions were specifically attributed to lemborexant by the investigators. Overall, there were no consistent findings suggesting an immunogenic response with lemborexant compared to placebo.

Table 79: Occurrences of Rash, Allergy/Allergic, or Hypersensitivity in the Phase 2 and 3 Database

Subject ID	Dose	Verbatim	MedDRA term
001-(b) (6)	LEM15/25	Rash on face, neck and left leg, where tape had been applied	Dermatitis, contact
201-(b) (6)	LEM15/25	Maculopapular rash	Rash maculo-papular
303-(b) (6)	LEM10 Day 22	Unknown Allergy	Hypersensitivity
303-(b) (6)	LEM10 Day 50	Rash-Bilateral Arm	Rash
303-(b) (6)	LEM10 Day 114	rash on face, neck and neckline (allergic reaction)	Dermatitis allergic
303-(b) (6)	LEM10 Day 214	Rash	Rash

Subject ID	Dose	Verbatim	MedDRA term
303-(b) (6)	Placebo	Allergic reaction to Bactrim, full body rash	Drug hypersensitivity
201-(b) (6)	Placebo	Rash	Rash

Source: Clinical Reviewer generated table based on the Applicant-submitted phase 2 and 3 safety database (120-Day Update)

Clinical Reviewer Comments*: With 1,418 subjects exposed to lemborexant in the development program, lemborexant does not appear to cause clinically meaningful immunogenicity. With no immunogenicity observed in 1,418 subjects, the upper bound of the 95% CI would be ≈ 1/(1,418/3) = 1/472 ≈0.2% based on the Rule of 3.*

8.2.5. Analysis of Submission-Specific Safety Issues

As explained in Section 8.2.1.3, the following submission-specific safety issues were identified: 1) somnolence; 2) potential consequences of somnolence (next day residual impairment and middle of the night safety); 3) suicidal ideation and behavior; 4) parasomnia and complex sleep behaviors; 5) cataplexy; 6) fractures; 7) falls; and 8) abuse liability, including overdose, drug abuse potential, withdrawal, and rebound.

8.2.5.1. Somnolence

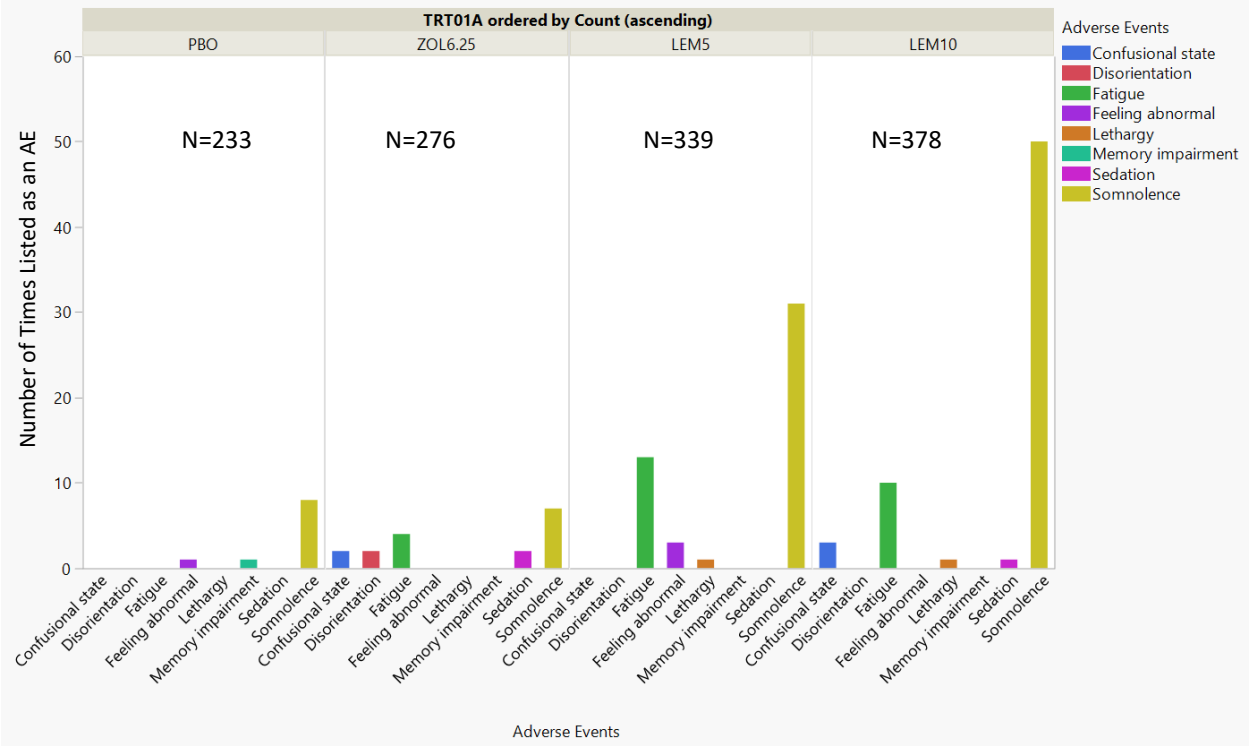
Summary: Somnolence was a prespecified AE of interest by both the Applicant and the clinical review team. Somnolence was the most common AE in the phase 3 studies, and was dose-related (6.9% and 11.2% for lemborexant 5 and 10 mg, respectively, vs. 1.7% for placebo, Source: ISS 120-Day Update, Table 8) and the most common treatment emergent adverse event leading to discontinuation in phase 3 studies. The incidence of discontinuation due to somnolence was 0.7% for LEM5, 1.0% for LEM10, and 0.4% for placebo during the first 30 days, and 1.1% for LEM5, 2.3% for LEM10, compared to 0.6% for PBO in the Phase 3 Pool (Source: ISS 120-Day Update Table 21). There was a small number of cases of persistent somnolence during the 14 day follow-up period after discontinuation of study drug: 1 (0.1%) LEM5 and 3 (0.4%) LEM 10, compared to zero with placebo.

Clinically, the term somnolence is reserved for a state of strong desire for sleep. However, there was no specified definition for somnolence in the lemborexant drug development program; as such, it may represent a broad construct (e.g., may refer to any time of day or may refer to fatigue, or another term related to sleepiness that tends to be less impairing). Therefore, this clinical review assesses the incidence of occurrence of the MedDRA preferred term somnolence as well as related terms.

Incidence of Somnolence and Fatigue and Other Terms Related to Somnolence: A number of preferred terms are related to somnolence, and/or may indicate somnolence. Such terms include fatigue, lethargy, sedation, disorientation, and confusional state. Figure 48 shows the numbers of times these preferred terms were reported as an adverse event, by treatment group, in the phase 3, 30-day pool. The bar height is not corrected for the sample size in the

treatment groups; nevertheless, the relationship between the occurrence of somnolence and related terms is clear.

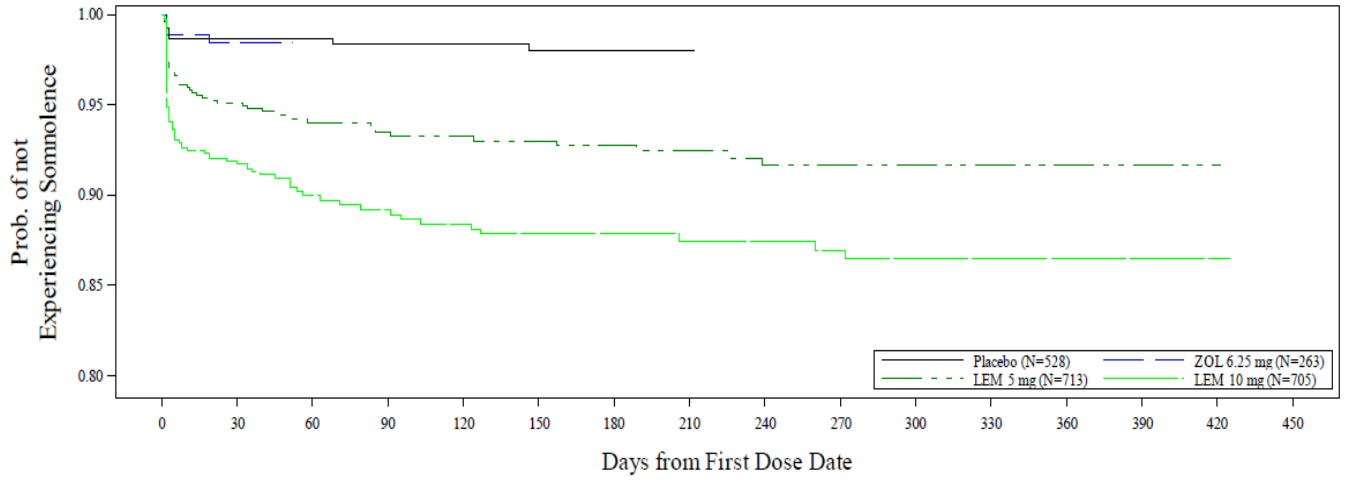
Figure 48: Occurrence of Somnolence-Related MedDRA Preferred Terms by Treatment Arm, Phase 3 30-Day Pool



Abbreviations: LEM, lemborexant; PBO, placebo; ZOL, zolpidem
Source: Clinical Reviewer generated table from the Phase 3 30-Day Pool

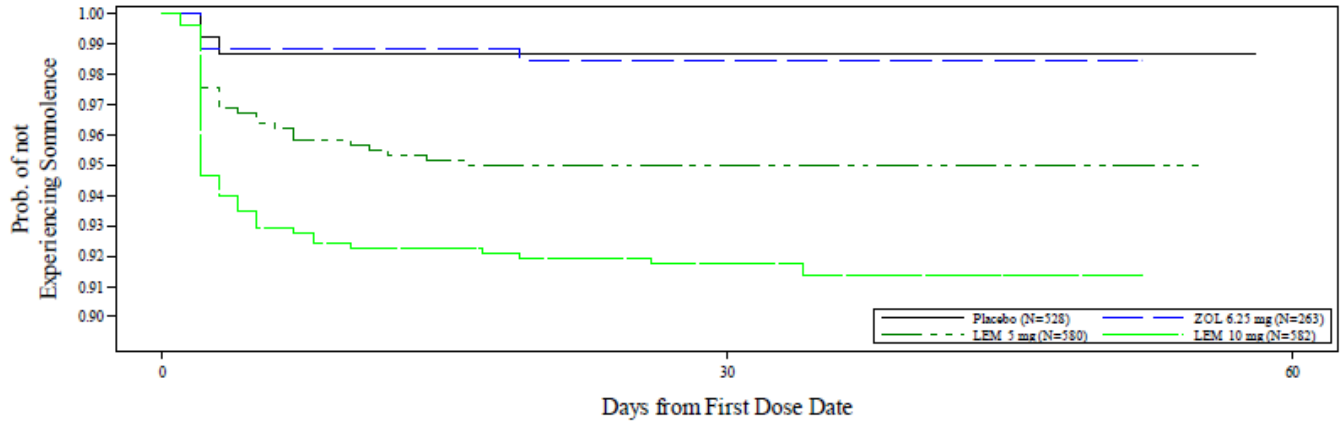
Time to Somnolence: To examine the time to the first event of somnolence, Kaplan-Meier estimates were reviewed. Time-to-first onset was defined as the time from the first dose date to the first day of onset for any TEAE of somnolence. If a subject did not experience somnolence, the subject was censored at last dose or last known visit date (whichever is earlier) +14 days for each treatment group. Figure 49 illustrates that lemborexant's somnolence tends to appear early, with limited additional somnolence occurring later in the treatment course. Figure 50 limits results to the first 60 days to allow for better visualization in the early treatment period.

Figure 49: Kaplan-Meier Estimates of First Time to Have Somnolence, Phase 3 Pool



Source: Applicant's 120-Day Update, Figure 4.1.6.1

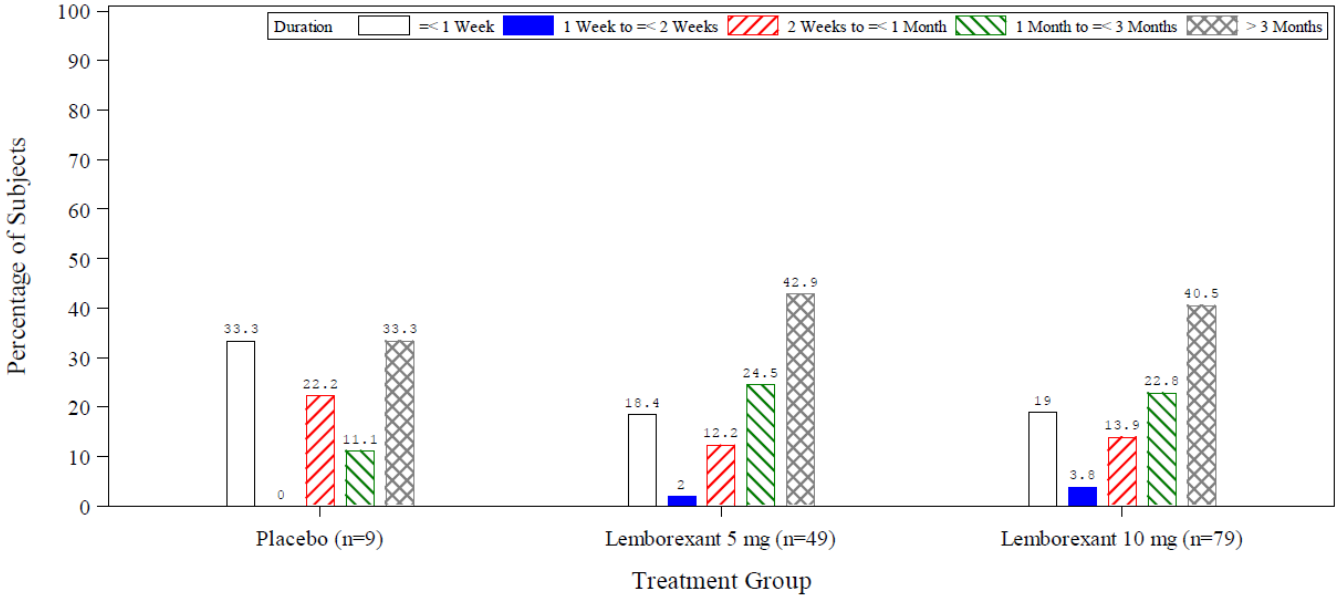
Figure 50: Kaplan-Meier Estimates of First Time to Have Somnolence Up to 60 Days, Phase 3 Pool



Source: Applicant's Lemborexant Month 1 Safety, Figure 4.1.6.1

Next, the duration of somnolence was considered by treatment group. Duration of somnolence was calculated as the sum of the duration of all somnolence events for each subject and treatment group. Figure 51 shows that for subjects reporting somnolence, it tended to persist, with some 40% of patients reporting a duration in excess of 3 months. The duration was shorter for the placebo group than the lemborexant groups. The duration of somnolence was similar for lemborexant 5 and 10 mg.

Figure 51: Somnolence by Duration and Treatment Group in Phase 3 Pool



Source: Applicant's 120-Day Update, Figure 4.1.6.2

Elderly Subjects: Somnolence was examined by age because elderly patients can have increased sensitivity to the adverse reactions of hypnotic drugs. Table 80 lists the incidence of somnolence by age group for the first 30 days of studies 303 and 304, and for the Phase 3 Pool, which contains data for up to 12 months. The data suggest that patients above the age of 65 may be more likely to experience somnolence with the higher (10-mg) dose of lemborexant than patients <65 years of age.

Table 80: Incidence of Somnolence by Age in the Phase 3 Pools, First 30-Days and Up to 12 Months

Somnolence Phase 3 Pool, First 30-days Only					
	Placebo n/N(%)	LEM5 n/N(%)	LEM10 n/N(%)	Total n/N(%)	ZOL ER 6.25 mg n/N(%)
Age <65	5/346 (1.4)	19/375 (5.1)	29/377 (7.7)	48/752(6.4)	3/143 (2.1)
Age ≥65	2/182 (1.1)	10/205 (4.9)	20/205 (9.8)	30/410(7.3)	1/120 (0.8)
Somnolence Phase 3 Pool, Data up to 12 months					
		LEM5 n/N(%)	LEM10 n/N(%)	Total n/N(%)	
Age <65		26/320 (11.8)	37/313 (8.1)	63/633 (10.0)	
Age ≥65		12/127 (9.4)	23/124 (18.5)	35/251 (13.9)	

Source: Clinical Reviewer generated table using data from the ISS month-1-tables file, Table 7.1.1.2, and the Applicant's Study 303 Study Body, Table 14.3.1.3.3.2 and the ISS 120-Day Update, Table 7.1.1.3).

***Clinical Reviewer Comments**: Somnolence was the most common adverse reaction to lemborexant in the development program. It was more frequently reported in subjects ≥65 years in the lemborexant 10 mg treatment arm compared to individuals younger than 65 or subjects in the lemborexant 5 mg group. For those who reported somnolence, somnolence tended to*

occur within the first 30 days of treatment and then continued for months. Somnolence could be associated with other factors, such as postural stability, impaired attention, and potentially an increased risk of falls, especially in the elderly. Therefore, inclusion of a cautionary statement related to somnolence is warranted for the label.

8.2.5.2. Next-Day Residual Impairment

Summary: The Applicant assessed the effect of lemborexant on next-day impairment, including next-day subjective sleepiness, morning sleep propensity (objective), and next-day cognition and motor impairment, including driving performance. For most studies, there were no clinically meaningful effects of lemborexant on next-day impairment compared to placebo. A description of the Applicant's results follows:

8.2.5.2.1. Next Day Sleepiness and Sleep Propensity

Next-Day Subjective Sleepiness
Studies 001 Part B, 002, 003, and 201 measured subjective sleepiness using the Karolinska Sleepiness Scale (KSS) administered shortly after morning waketime at approximately 8 hours. The KSS is a self-rated assessment of sleepiness. In some studies, the KSS was rated at 15-minute, 1 hour, and 2-hour time points. Higher scores reflect feeling more sleepy.

In Study 002, there were no meaningful trends observed for LEM2.5 or LEM5 on the KSS, although in the first few days there was an adverse trend for lemborexant 10 mg vs. placebo during the first 2 hours after morning awakening; this trend waned after a few days.

In Study 201, when subjective sleepiness was measured at 15 minutes, 1 hour, and 2 hours after morning waketime, there were no significant increases in KSS ratings at lemborexant doses up 10 mg after either the first 2 doses or the last 2 doses.

Lemborexant doses higher than the to-be-marketed dose (15 and 25 mg) caused significant increases in subjective sleepiness (KSS) compared to placebo. At doses of 25 mg and higher, i.e., more than double the to-be-marketed dose, increases in KSS ratings were larger in magnitude than for the 10-mg dose and lasted ~ 8 hours after morning waketime.

Objective Morning Sleep Propensity
Morning Sleep Propensity was examined using the Multiple Sleep Latency Test (MSLT) after subjects awakened from overnight PSG. The test consisted of a series of nap opportunities from which SOL was measured. Shorter SOL represents greater morning sleep propensity. In Study 107, a modified MSLT (M-MSLT) was used, such that a total of 4 sleep latency tests were performed, starting 45 minutes after morning waketime, with subsequent sleep latency tests occurring at 30-minute intervals. Subjects with insomnia were assigned to randomized treatment sequences of a single dose of placebo, LEM5, and LEM10 in a double-blind crossover manner, followed by flurazepam (included for assay sensitivity) in an open-label manner, prior to overnight PSG and M-MSLT, with a washout period between each administration. The

Applicant states the primary objective was to rule out a clinically meaningful effect on SOL, defined as a mean baseline SOL after evening administration of lemborexant of not more than 6.0 minutes shorter than PBO. For lemborexant 5 and 10 mg, the LS-mean differences from placebo were -1.15 and -3.48 minutes (Source: Study 107 Study Report, Table 12). For flurazepam, mean SOL was > 6 minutes shorter than placebo. The lower bound of the 95% CI for LEM5 and LEM10 was not greater than 6 minutes, suggesting that there was no clinically meaningful effect of next-morning residual sleepiness for lemborexant as measured by M-MSLT. Subgroup analyses by sex, age group (<65 years and ≥65 years), and BMI showed that the lower bound of the 95% CI exceeded 6 minutes (6.09 minutes) in the lemborexant 10-mg male subgroup. Other subgroups did not exceed this threshold.

Clinical Reviewer Comments*: Objective and subjective measures suggest that some subjects experienced next-day sleepiness with lemborexant. However, results were not consistent. The report of next-day sleepiness is seen in other drugs used to treat insomnia.*

8.2.5.2.2. Next-Day Cognition and Motor Impairment, Including Driving Performance

Several objective tests were conducted to measure next-day cognition and motor impairment, as described below:

Cognition: Effect of lemborexant on next-day cognition (memory and attention) was assessed in Study 108 (single dose, healthy subjects) and 304 (phase 3 study, subjects with insomnia disorder) using the Performance Assessment Battery (PAB) that was administered the morning after awakening. Notably, all subjects in Studies 108 and 304 were age 55 or older. The PAB consists of nine tasks that take approximately 30 minutes to complete. The results are organized into four domain factor scores (power of attention, continuity of attention, quality of member, speed of memory retrieval). In Study 304 when assessed at 8 hours post-dose on Day 30/31, there was no clinically meaningful impact on Continuity of Attention, Quality of Memory, or Speed of Memory Retrieval at either the beginning or the end of the treatment period. The only meaningful difference in the mean change from baseline was for a slower performance the Power of Attention domain for LEM5 and LEM10, compared to PBO at both Days 2/3 and Days 30/31 (Source: Study 304 CSR, Table 14.2.2.18). For Study 108, LEM10 showed clinically meaningful threshold of impairment for Power of Attention only (Source: Study 108 CSR, Table 14.2.5.4.1). Subjects on lemborexant performed better than placebo on quality of memory testing in Study 108. There was a decrease in speed of memory retrieval, but this was not different than placebo.

Next-Day Digit Symbol Substitution Test (DSST): Study 002 showed that there were no meaningful effects observed on mean scores for the DSST in subjects taking LEM5 or LEM10. Rather, mean scores on the DSST generally increased from Baseline, suggesting the insensitivity of this assessment, including a practice or learning effect, rather than impairment.

Next-Day Psychomotor vigilance test (PVT): Assessment of objective sleepiness using the PVT in Study 002 showed no meaningful effects on mean scores for the PVT in the LEM5 dose group. Slight differences compared to placebo were observed in LEM10 on PVT lapses (defined as reaction time >500 msec). In the LEM10 cohort, the small increase in objective sleepiness as measured by PVT lapses was relatively greater on Days 2 to 4 than on Days 5 to 15, suggesting that this small effect diminished after the first few treatment days.

Next-Day Reaction Time Index (RTI): The RTI measures reaction time as a proxy for sleepiness after awakening. RTI was measured at 15 minutes, 1 hour, and 2 hours after waking on study Days 2/3 and 15/16. Lemborexant was compared to placebo for a range of doses (1, 2.5, 5, 10, 15, and 25 mg). The data from this study showed no clinically meaningful differences from placebo and no dose-response (Source, Study 201 CSR, Table 33).

Next-Day Postural Stability: Studies 108 and 304 measured postural stability immediately upon getting out of bed at the end of an 8-hour PSG recording (8 hours postdose). Postural stability was measured by assessing body sway using an ataxia meter. The mean scores for middle of the night (MOTN) postural stability was reviewed in Studies 108 and 304 and there were no clinically meaningful effects for lemborexant 5 or 10 mg compared to placebo.

Next-Day Driving Performance: Section 6.3.2.4 describes the results of the driving performance study, Study 106, in detail. Per the Applicant, Study 106 followed the FDA Guidance for Industry on Evaluating Drug Effects on the Ability to Operate a Motor Vehicle. In brief, Study 106 was a randomized, double-blind, placebo- and active-controlled, four-period crossover study evaluated the effects of nighttime administration of lemborexant on next-morning driving performance approximately 9 hours after dosing in 24 healthy elderly patients (≥65 years old, median age 67 years; 14 men, 10 women) and 24 adult patients (median age 49 years; 12 men, 12 women). Subjects operated a specially instrumented vehicle (not a simulation) for approximately 1 hour over a 100-km primary highway circuit with an instructor who had access to dual controls of the brakes and accelerator. Speed and lateral position were continuously recorded. The primary outcome measure from the study was standard deviation of the mean lateral position across the 100-km drive (SDLP). The primary driving performance outcome measure was change in SDLP. A blood alcohol level at the legal limit of 0.5 g/L has been shown to produce a mean change in placebo-corrected SDLP of 2.4 cm. Testing was conducted after one night (a single dose) and after eight consecutive nights of treatment with lemborexant. Results suggest that lemborexant at doses of 5 and 10 mg did not cause clinically meaningful impairment in next-morning driving performance in adult or elderly patients (mean findings compared with placebo). However, there was a range of findings and driving ability was impaired in some subjects taking LEM10. No subjects stopped the study prematurely. Findings will be used to inform label warnings and precautions accordingly.

Clinical Reviewer Comments*: Several objective measures were used to assess the potential for next day impairment. Most were described as secondary or exploratory by the Applicant. Findings suggest that attention and psychomotor reactions may be affected in the morning*

following lemborexant for some individuals. However, the sum of these results were not considered clinically meaningful because of inconsistencies and a lack of dose-response, even when high doses of lemborexant were tested. Yet, potential safety concerns exist due to the range of impairment seen, as noted in the driving study. Given the potential safety signal for some patients, caution regarding daytime impairment and driving warrant inclusion in the label.

8.2.5.3. Middle of the Night (MOTN) Safety:

Summary: The primary study to assess MOTN safety for lemborexant was Study 108, a randomized, placebo- and active-controlled trial in healthy female subjects ≥ age 55 or male subjects ≥ age 65. Middle of the night postural stability, awakening to sound, and cognitive performance were tested. Overall, there were several clinically meaningful findings to suggest that lemborexant does have an effect on postural stability compared to placebo. An overview of results presented in the Study 108 CSR follows:

MOTN Postural Stability:
In Study 108, postural stability, the ability to awaken in response to a sound stimulus, and cognition (attention and memory) were assessed following a scheduled awakening 4 hours after the start of the time in bed. As above, postural stability was measured by assessing body sway using an ataxia meter. A higher number indicates more body sway and less postural stability. The Applicant states that a 7-unit increase in body sway (postural stability) has been associated with a 0.5 g/kg dose of alcohol. In Study 108, The placebo-subtracted least squares mean difference (LSMD) for body sway at 4 hours post-dose change from baseline (95% CI) was 6.8 (1.2, 12.3) for LEM5 and 9.3 (3.7, 14.8) for LEM10.

MOTN Awakening to Sound:
The ability to awaken to sound was assessed using an audiometer that delivered 1000 Hz tones up to 105 dB. There were no meaningful differences between lemborexant (5 or 10 mg) and placebo on ability to awaken to sound.

MOTN Cognitive Performance:
A computerized performance assessment battery (PAB) was administered to assess cognitive performance, which was measured during MON testing. The threshold for clinically meaningful effects was based on estimates from the effect of a 0.5 g/kg dose of alcohol. The Applicant prespecified meaningful change as follows: power of attention, LSMD from baseline of 48.8 msec; and quality of memory LSMD 32.57.

The LSMD and 95% CI were calculated between active dose and placebo for power of attention, continuity of attention, quality of memory, and speed of memory retrieval. Data are presented in Table 81. Clinically meaningful changes from baseline were observed for all four domains tested. Note that changes on cognitive performance are dose related, and LSM differences from placebo are nominally statistically significant in some cases.

Table 81: Results From Middle of the Night Safety Testing of Cognition (Attention and Memory) in Study 108

Cognitive Domain	LEM5 N=56 LSMD* (95% CI)	LEM10 N=56 LSMD* (95% CI)
Power of attention (msec; higher values reflect impairment)	73.0 (-28.5, 174.5)	202.2 (100.8, 303.7)
Continuity of attention (units; lower values reflect impairment)	-1.1 (-2.5, 0.3)	-2.9 (-4.3, -1.5)
Quality of memory (units; lower values reflect worse performance)	-12.7 (-30.4, 5.1)	-34.6 (-52.3, -16.8)
Speed of memory retrieval (msec; higher values reflect worse performance)	213.8 (-4.1, 431.6)	305.8 (88.0, 523.6)

*Least squares mean difference from placebo, Placebo N=56
Source: Clinical Reviewer table created using free text and data from Study 108 Study Report, Table 16, 17, 18, 19.

Clinical Reviewer Comments*: All findings for the cognitive domain separated from placebo for the 10-mg dose of lemborexant and appear to have reached the prespecified level of meaningful change as specified by the Applicant. The units for the computerized performance assessment battery present a challenge for clinical interpretation. However, findings for lemborexant 10-mg suggest that impairment in attention and memory can occur when measured at approximately 4 hours postdose.*

8.2.5.4. Suicidal Ideation and Behavior

Suicidal ideation and behavior was measured using the Columbia-Suicide Severity Rating Scale (C-SSRS). The Applicant notes there were no suicidal behavior events reported in any group in the all sleep disorders pool, which included phase 2 and 3 studies as well as patients with obstructive sleep apnea.

Table 82 summarizes C-SSRS data from the all insomnia pool at baseline, end-of-treatment (EOT), and end-of-study (EOS). A subject was counted once for each category if at least one question was answered positive in that category. Results were similar for the all sleep disorders pool using C-SSRS. No suicidal behavior or self-injurious behavior was reported in any group.

Table 82: C-SSRS Endorsed Items, Result from the All Insomnia Pool

		Lemborexant				
C-SSRS Item	Placebo (N=596) n(%)	1 – 2.5 mg (N=72) N (%)	5 mg (N=751) N (%)	10 mg (N=747) N (%)	15 – 25 mg (N=118) N (%)	Total (N=1688) N (%)
Baseline						
Any suicidality	5 (0.8)	0	4 (0.5)	7 (0.9)	1 (0.8)	12 (0.7)
Any suicidal ideation	5 (0.8)	0	4 (0.5)	7 (0.9)	1 (0.8)	12 (0.7)
Any suicidal behavior	0	0	0	0	0	0
Self-injurious behavior	0	0	0	0	0	0
End of Treatment (EOT)						
Any suicidality	1 (0.2)	0	3 (0.4)	2 (0.3)	0	5 (0.3)
Any suicidal ideation	1 (0.2)	0	3 (0.4)	2 (0.3)	0	5 (0.3)
Any suicidal behavior	0	0	0	0	0	0
Self-injurious behavior	0	0	0	0	0	0
End of Study (EOS)						
Any suicidality	0	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Any suicidal ideation	0	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Any suicidal behavior	0	0	0	0	0	0
Self-injurious behavior	0	0	0	0	0	0

Abbreviation: C-SSRS, Columbia Suicide Severity Rating Scale
Source: Applicant ISS 120-Day Update, Table 25

Table 83 provides the Applicant's summary of C-SSRS findings in the LEM5, LEM10, and placebo groups in Study 303. For this analysis, the Applicant defined "suicidality" as the occurrence of any suicidal behavior or any suicidal ideation. Suicidal ideation was considered present if the answer to any of the following items was positive: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any method (not plan) without intent to act, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with specific plan and intent. Subjects with more than one positive answer were counted only once.

Considering the time course of positive responses (i.e., as many positive responses at baseline as during month 1, 3, or 6 of the study) and their low numbers, these data do not appear to provide a signal for suicidality for lemborexant.

Table 83: Summary of C-SSRS by Month of Treatment, Treatment Period 1; Study 303

	Lemborexant	Placebo	
	5 mg (N=314)	10 mg (N=314)	(N=319)
Baseline			
n	314	314	319
Any suicidality	3 (1.0)	4 (1.3)	3 (0.9)
Any suicidal ideation	3 (1.0)	4 (1.3)	3 (0.9)
Any suicidal behavior	0	0	0
Self-injurious behavior	0	0	0
Month 1			
n	307	310	315
Any suicidality	3 (1.0)	2 (0.6)	1 (0.3)
Any suicidal ideation	3 (1.0)	2 (0.6)	1 (0.3)
Any suicidal behavior	0	0	0
Self-injurious behavior	0	0	0
Month 3			
n	279	268	287
Any suicidality	1 (0.4)	1 (0.4)	0
Any suicidal ideation	1 (0.4)	1 (0.4)	0
Any suicidal behavior	0	0	0
Self-injurious behavior	0	0	0
Month 6			
n	262	245	270
Any suicidality	0	1 (0.4)	1 (0.4)
Any suicidal ideation	0	1 (0.4)	1 (0.4)
Any suicidal behavior	0	0	0
Self-injurious behavior	0	0	0

Abbreviation: C-SSRS, Columbia Suicide Severity Rating Scale
Source: Applicant's 303 Study Body Report Table 14.3.4.7.1

To expand upon the data presented by the Applicant, we conducted a review of preferred terms for adverse events related to suicidal ideation, suicidal thoughts, or behaviors in studies 303-Core and 304. No related preferred terms were noted. The only similar preferred term was "morbid thoughts," listed in one patient, without elaboration or narrative.

To further assess for a safety signal with lemborexant, the safety review team completed an independent analysis of the C-SSRS item "Wish to Die," completed during Studies 303 and 304. Data from these studies are presented in Table 84. Results demonstrate that the numbers of individuals endorsing "wish to die" was low and not meaningfully different than placebo.

Table 84: Subjects Endorsing "Wish to Die" on the C-SSRS in Studies 303, 304, and Combined

	Endorsed on Drug n/total (%)	Endorsed on Placebo n/total (%)	*p*-value
Study 303	8/1771 (0.5)	1/898 (0.1)	0.15
Study 304	4/538 (0.7)	3/207 (1.5)	0.38
Combined 303 & 304	12/2309 (0.5)	4/1105 (0.4)	0.60

8.2.5.5. Parasomnias and Complex Sleep Behaviors

Overview: The International Classification of Sleep Disorders (ICSD) includes the following symptoms under the umbrella term parasomnia: confusional arousals, sleepwalking, sleep terrors, sleep-related eating disorders, sleep paralysis, nightmare disorder, exploding head syndrome, sleep-related hallucinations, somnambulism, and sleep enuresis (see [32] for review). Therefore, to ensure the review of safety adequately considered potential parasomnias, the phase 3 studies were recoded to match the MedDRA-terms that match the ICSD parasomnias. For example, the verbatim phrasing "patient describes sensation of 'loud clanging in his head' occurring after taking IP whilst lying in bed before falling asleep" was recoded to "exploding head syndrome," which is a form of parasomnia.

The decision to broaden the review of sleep paralysis to include other terms that fall under parasomnia was made because, in 2019, the FDA added a Boxed Warning and a Contraindication related to parasomnias to several drugs indicated for the treatment of insomnia. The Boxed Warning describes the possibility of serious injuries and death due to complex sleep behaviors. The contraindication states to avoid use in patients who have previously experienced an episode of complex sleep behavior. Notably, complex sleep behavior is type of parasomnia, defined as "complex activities, normally associated with wakefulness, that occur when the subject is in a sleep-like state after taking a hypnosedative drug; when the subject awakens the next morning, the subject has little or no memory of the activity [33]."

Because the prevalence of parasomnia is relatively rare with drugs used to treat insomnia, we searched for any MedDRA term related to parasomnia across the phase 2 and phase 3 safety database. Table 85 shows the frequencies of any parasomnia term in the combined phase 2 and phase 3 safety database; frequencies were 3.4% and 6.6% for lemborexant 5 and 10 mg, respectively, and 4.8% for placebo. Moreover, across the range of doses studied (1/2.5 mg to 15/25 mg), the incidence of parasomnia was dose-related.

Table 85: Incidence of Parasomnia Related Terms in the Phase 2 and Phase 3 Safety Database

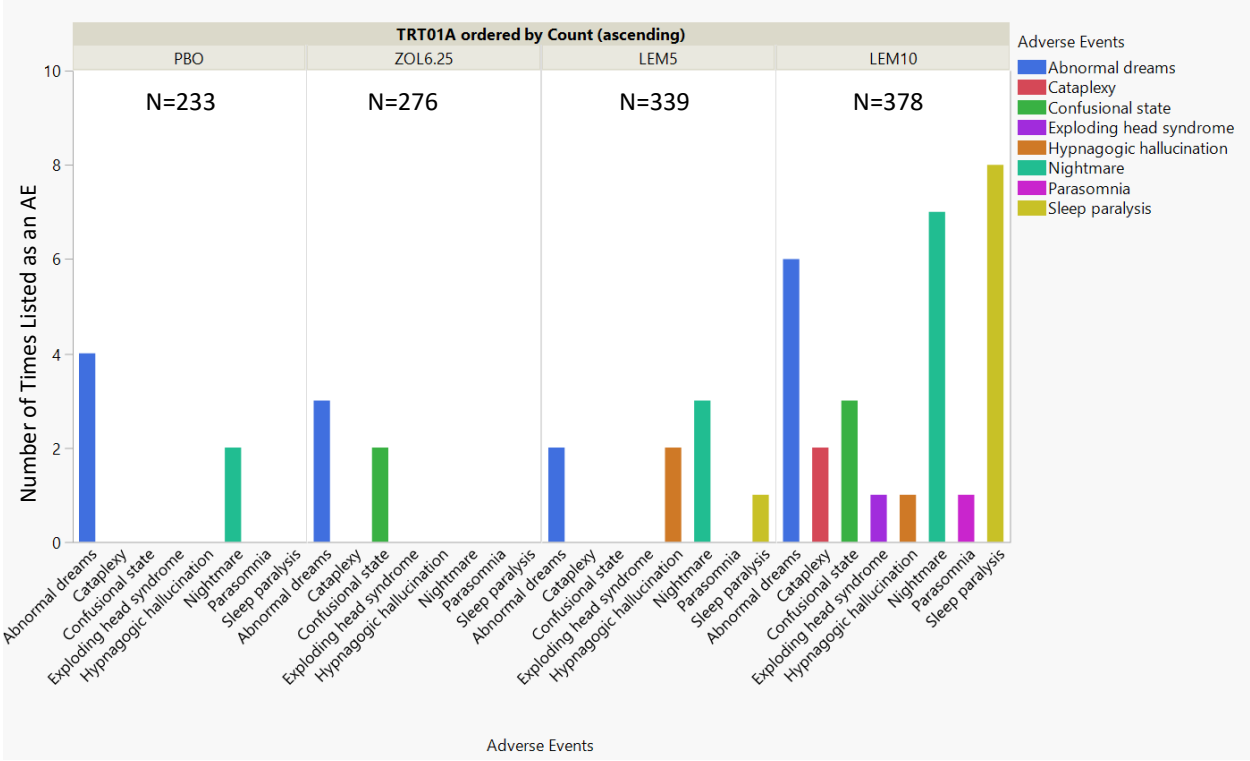
MedDRA term	**Placebo** N=1036 n (%)	**LEM1/2.5** N=67 n (%)	**LEM5** N=1109 n (%)	**LEM10** N=1064 n (%)	**LEM15/25** N=197 n (%)	**ZOL** 6.25/10 N=288 n (%)
Total	50 (4.8)	2 (3.0)	38 (3.4)	70 (6.6)	19 (9.6)	4 (1.4)
Abnormal dreams or nightmare	17 (1.6)	2 (3.0)	19 (1.7)	27 (2.5)	6 (9.6)	3 (1.0)
Complex Sleep Behavior	0	0	0	2 (0.2)	0	0
Exploding head syndrome	0	0	0	1 (<0.01)	0	0
Hypnagogic hallucination	18 (1.7)	0	7 (0.6)	9 (0.8)	3 (1.5)	1 (0.3)

Hypnopompic hallucination	1 (<0.01)	0	0	1 (<0.01)	0	0
Parasomnia	0	0	0	1* (<0.01)	0	0
Sleep Paralysis	14 (1.4)	0	12 (1.0)	31 (2.9)	10 (0.5)	0
Somnambulism	0	0	0	1 (<0.01)	0	0

*Complex sleep behavior
Abbreviations: LEM, lemborexant; ZOL, zolpidem
Source: Clinical Reviewer generated table from ISS 120-Day safety update, phase 2 and phase 3 studies, adae.xpt

To visualize the occurrence of MedDRA terms that may be associated with parasomnias, Figure 52 was created using the phase 3, 30-day pool by treatment arm (the bar heights were not corrected for subject number in each arm). The graph suggests that the overall counts of parasomnia-related terms are low for each treatment arm (none more than 8 times) but appear to be more frequent in the LEM10 group compared to placebo. Sleep paralysis, nightmares, and abnormal dreams are the most commonly represented terms.

Figure 52: Occurrence of Parasomnia-Related MedDRA Preferred Terms by Treatment Arm, Phase 3 30-Day Pool



Abbreviations: LEM, lemborexant; PBO, placebo; ZOL, zolpidem
Source: Clinical Reviewer generated table from the Applicant's ISS 30-Day Pool

Complex Sleep Behavior: A review of the verbatim terms in the phase 2 and phase 3 safety database revealed one subject ([redacted] (b) (6)) who described a complex sleep behavior: "Vivid dreams: the patient refers to experience vivid dreams. One week ago she woke up and she was acting the dream (she was acting to write a letter)". This patient was a 51 year old female in the

LEM10 group of Study 303. No narrative was located for this subject. The verbatim term was appropriately translated to the MedDRA term parasomnia.

Additionally, the Applicant stated that one incidence of somnambulism was considered a complex sleep behavior. Subject (b) (6) was a 66-year-old white female in the LEM10 group of Study 303. On study day 315, the patient had a single event described in the narrative as "somnambulism" between 1 AM and 2 AM, moderate in severity, and related to study drug. She had no previous history of somnambulism or other events listed in the narrative.

No reports of complex sleep behavior were noted in the placebo groups for phase 2 or 3.

Clinical Reviewer Comments*: The percentage of subjects reporting a parasomnia was small but notable because of the serious safety concerns related to complex sleep behaviors (e.g., driving a car) that have been reported with other drugs. Two incidents of complex sleep behavior were reported, without associated harm. These findings will be used to inform label warnings and precautions. Notably, the FDA recently added warnings for complex sleep behaviors to many hypnotic drugs, and the matter remains under review.*

8.2.5.6. Cataplexy and Potential Cataplexy

Cataplexy was identified as a program-specific TEAE. TEAEs related to cataplexy included cataplexy, potential cataplexy (as defined by MedDRA query), and any additional events identified by an investigator as potential cataplexy in the clinical report forms. All TEAEs related to cataplexy were adjudicated by an independent adjudication committee blinded to treatment group.

Given the rarity of cataplexy, we reviewed all data from the all sleep disorders pool for the mention of cataplexy or potential cataplexy. In the all sleep disorders pool, the incidence of cataplexy and potential cataplexy was similar in all groups. There was total of 62 subjects with MedDRA terms related to cataplexy (11 [1.5%] subjects in the PBO, 23 [2.8%] subjects in the LEM5, 24 [2.7%] subjects in the LEM10, and 4 [3.0%] subjects in the LEM15 to 25 groups). Of these subjects, 1 subject ((b) (6) had a preferred term event of cataplexy that was initially listed as adjudicated as cataplexy in the ISS 120-Day safety update (but later the Applicant stated this was a typo and the case was not agreed upon by the adjudication committee). The details of the cataplexy-like event for subject (b) (6) are presented below:

> Subject (b) (6) was a 56 year old male in the LEM10 group of Study 303. The subject discontinued the study on Day 133. Per report, the subject attributed fatigue and depression to the study drug and wanted to discontinue/withdrawal. The cataplexy-like events occurred on study days 2 and 20, both categorized as mild, related, and recovered/resolved. The narrative includes the following event details:
>
> Study Day 2: There were no reported warning signs before the event. The subject experienced sudden bilateral weakness of knees and legs at the onset of the event or

during the event. The event lasted for less than 2 seconds with tension, stress and sleepy feeling and the subject was awake throughout the event. After the event, the subject had a drained feeling and the bilateral weakness gradually returned to normal. The symptoms resolved on the same day. The subject reported feeling awake after the event.

Study Day 20: The subject experienced the second event of cataplexy. The event was determined by the investigator to be nonserious, mild in severity, and related to study drug. No treatment was reported for this event. No action was taken with the study drug in response to the event and the treatment with the study drug continued. There were no warning signs noticeable before the event. The subject reported sudden weakness in both knees and legs; the subject was awake throughout the event. The event lasted for less than 2 seconds with tension, stress and sleepy feeling. After the event, the subject had a drained feeling and the bilateral weakness gradually returned to normal. The symptoms resolved on the same day.

Clinical Reviewer Comments*: The description of Subject* (b) (6) *is similar to a clinical report of cataplexy. However, the independent review committee that reviewed the full details of the case did not reach consensus and Subject* (b) (6) *was not categorized as having experienced cataplexy. Therefore, no cataplexy events were reported in the lemborexant development program.*

8.2.5.7. Fractures

Given the potential for drug-related changes on bone, a special review was undertaken for fractures.

The high-dose animal studies are summarized in Section 5.5 and Table 15. The overall incidence of fractures was reviewed in during the first 30-days of the phase 3 trials and in the combined phase 2 and phase 3 trials.

Table 86 shows the overall incidence of any bone related events and falls, by MedDRA preferred term. Because MedDRA terms code fracture by anatomical location, the incidence of any fracture was combined to examine the overall incidence of fractures in the phase 3 pool and the combined phase 2 and 3 dataset. The frequencies of fracture were similar in the lemborexant 5- and 10-mg groups and the placebo group.

Table 86: The Overall Incidence of Fractures, Phase 3 Pool, Combined Phase 2 and 3 Database

Phase 3 studies (Study 303 and 304)						
	Placebo N=528 n (%)		LEM5 N=713 n (%)	LEM10 N=705 n (%)		ZOL6.25 N=263 n (%)
Fracture	7 (1.3)		7 (0.9)	6 (0.9)		0

and MedDRA terms	1 rib 1 foot 1 hand 1 wrist 1 pelvic 1 sternal 1 tibia		1 foot 1 ankle 1 lower limb 3 hand 1 wrist	1 rib 1 foot 1 ankle 1 lower limb 1 Radius 1 upper limb		
Combined Phase 2 and 3 Dataset						
	Placebo N=1036 n (%)	LEM 1/2.5 N=67 n (%)	LEM5 N=1109 n (%)	LEM10 N=1064 n (%)	LEM 15/25 N=197 n (%)	Zolpidem ER 6.25/10 N=288 n (%)
Fracture and MedDRA terms	10 (1.0) 1 ankle 1 hand 2 foot 1 pelvic 2 rib 1 sternal 1 tibia 1 wrist	none	8 (0.7) 1 ankle 4 hand 1 foot 1 lower limb 1 wrist	6 (0.6) 1 foot 1 lower limb 1 radius 1 rib 2 upper limb	none	none

Abbreviations: LEM, lemborexant; ZOL, zolpidem
Source: Clinical Reviewer generated table using data from ISS 120-Day update adae data file and ISS 120-Day Update, Appendix 2 4.1.4.7.

Serious adverse events related to bone and falls: The serious adverse events were reviewed for bone-related reports. Four cases of osteoarthritis, two falls, and 5 fractures were considered serious adverse events in the lemborexant 5 or 10 mg treatment arms. One rib fracture and one pelvic fracture were described as a serious adverse events in the placebo group. There were no cases of osteoarthritis classified as serious adverse events in the placebo group.

Table 87 highlights the narrative summaries for fractures categorized as a serious adverse events. Notably, there is no indication that the events were preceded by neurological adverse events such as somnolence and there was no suggestion of new onset change in bone density.

Table 87: Narrative Summary for Fractures Categorized at Serious Adverse Events, Phase 3 Studies

Category	Demographics	Narratives
Subject (b) (6) tibia fracture Study E2006-G000-303	41 year-old Asian female	On study day 121, Subject fell after slipping on ice. The subject reported no warning signs, no loss of consciousness, lightheadedness, dizziness, or

Category	Demographics	Narratives
LEM5		muscle weakness prior to or after the fall. She was alert after the fall. The subject underwent surgical repair and recovered. Determined as not related to study drug.
Subject (b) (6) rib fracture Study E2006-G000-303 LEM10	80-year-old Asian male	On study day 188 (Day 14 of study drug, patient was PBO in Period 1), the subject fell off a stepladder during pruning resulting in a rib fracture and hospitalization. Subject reported no warning signs or weakness and was alert before and after the event. Treatment was medication only. The event was submitted to the adjudication committee. No updates were mentioned in the 120-Day ISS update.
Subject (b) (6) ankle fracture Study E2006-G000-303 LEM5	66-year-old Asian female	On study day 205, the subject fell while playing golf, fractured her ankle, and was hospitalized. Subject reported no warning signs or weakness and was alert before and after the event. The subject underwent surgical repair and recovered. The investigator reported the fall was "caused by subject's carelessness." No updates were mentioned in the 120-Day ISS update.
Hand Fracture LEM5	Unknown	Hand fracture is listed in the table of serious adverse events, but no narrative was found.

Source: Clinical Reviewer generated table from associated subject narratives

Note that the patient population was at higher risk of fractures, given the older age of the population studied (older by design in several studies), and the preponderance of females (over 70% were female). Epidemiological data in healthy populations notes that fractures increase with age, and age-adjusted rates are 49% higher for women than men [34].

Serious adverse events related to bone included osteoarthritis. However, osteoarthritis is more common in the elderly population, which comprised almost 40% of the sample. Therefore, conclusions cannot be drawn about the occurrence of serious adverse events listed as osteoarthritis.

Clinical Reviewer Comments*: The incidence of serious adverse events and adverse events related to fractures was similar for lemborexant and placebo. We find no safety signal for fractures.*

8.2.5.8. Falls

The Applicant reported that, across all lemborexant studies, a total of 39 subjects (10 PBO subjects, 17 LEM5 subjects, and 12 LEM10 subjects) reported TEAEs of fall. In Studies 303 and 304, three subjects discontinued from the study because of falls (0 Placebo, 1 LEM5, 2 LEM10).

Table 88 shows the incidence of falls in Study 303-Core, the Phase 3 Pool, and the All Insomnia Pool.

Table 88: The Incidence of "Fall" in Study 303-Core, Phase 3 Pool, and the All Insomnia Pool

Study 303-Core (6 months, Placebo-Controlled)						
MedDRA term	Placebo N=319 n (%)		LEM5 N=314 n (%)	LEM10 N=314 n (%)		
Fall	10 (3.1)		5 (1.6)	5 (1.6)		
Phase 3 Pool (Study 303 and 304)						
	Placebo N=528 n (%)		LEM5 N=713 n (%)	LEM10 N=705 n (%)		ZOL6.25 N=263 n (%)
Fall	10 (1.9)		16 (2.2)	10 (1.4)		0
All Insomnia Pool (Studies 001 Part B, 107, 201, 303, and 304)						
	Placebo N=664 n (%)	LEM 1/2.5 N=72 n (%)	LEM5 N=820 n (%)	LEM10 N=815 n (%)	LEM15/25 N=118 n (%)	ZOL ER 6.25 N=263 n (%)
Fall	10 (1.5)	0	16 (2.0)	10 (1.2)	0	0

Abbreviations: LEM, lemborexant; PBO, placebo; ZOL, zolpidem
Source: Clinical Reviewer generated table using data from ISS 120-Day Update, Appendix Table 2, Table 4.1.2.1, Table 4.2.2.1

For the overall phase 3 database, the rates of falls were 5.0 and 3.2 per 100 patient-years in patients who received 5 and 10 mg lemborexant, respectively, and 6.3 in the placebo group (data not shown).

To explore whether there may be a signal for falls that was lost in the process of coding verbatim terms to preferred terms, the clinical team conducted the following analysis: for studies 303 and 304, the verbatim adverse events columns were searched for terms "fall," "falling," "fell." Duplicate events were removed, as were events not related to a physical fall (e.g., falling asleep). It was noted that, on numerous occasions, the verbatim adverse event terms combined incidence of falls with another term, but the Applicant did not include "Fall" as a MedDRA term for that adverse event. For example, an adverse event with the verbatim term "Right Knee Pain from fall" was translated to the preferred term "Joint injury," but not the preferred term "Fall."

In Study 304, there were 4 unique subjects who experienced falls, all on LEM5 (1.4%). One fall occurred during the follow-up period. In Study 303-Core, there 19 subjects experienced a fall,

but mostly in the placebo group: placebo 10 (3.1%); LEM5 4 (1.3%); LEM10 5 (1.6%). Study 303-EXT was the 6-month extension where those in the placebo group were re-randomized to LEM5 or LEM10, and those on LEM5 or LEM10 stayed on those original doses. There were 12 subjects who experienced falls as follows:

- Placebo → LEM5: 4/133 (3%)
- LEM5 → LEM5: 4/118 (3.4%)
- LEM5 Total: 8/251 (3.2%)
- LEM10 → LEM10: 1/101 (1.0%)
- Placebo → LEM10: 3/125 (2.4%)
- LEM10 Total: 4/226 (1.8%)

Clinical Reviewer Comments*: Based on verbatim terms coded by subjects, lemborexant does not appear to increase the risk of falls. There were no meaningful differences in incidence across the groups, and there was no evidence of a dose-response. Because hypnotics are associated with increased risks of falls, however, a general warning about falls is warranted for the lemborexant label.*

8.2.5.9. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Agency's Controlled Substance Staff (CSS) reviewed the nonclinical and clinical abuse-related data submitted by the Applicant for NDA 212028. The CSS team's review of non-clinical data suggested that lemborexant does not produce physical dependence or rewarding effects sufficient to maintain reinforcement in animals. However, studies in humans suggest that lemborexant was more likely than placebo to produce effects on drug liking, overall drug liking, and good drug effect. These effects were similar to the positive control drugs at higher doses (zolpidem 30 mg and suvorexant 40 mg), both of which are Schedule IV drugs.

The Applicant's reported results related to abuse liability are presented below.

Overdose: A TEAE of overdose was reported in 8 subjects in the lemborexant studies (5 intentional; 3 accidental). For intentional overdose, one subject received PBO (Subject (b) (6) and four subjects ((b) (6) (b) (6) (b) (6) (b) (6) received LEM5 (a 1-subject increase in the LEM5 group compared to the ISS). The maximum overdose was 10 mg per day and was not indicative of abuse potential. None of the intentional overdoses were associated with suicidality or self-injurious behavior, and no TEAEs were reported associated with these events (Source: ISS 120-Day Safety Update, Table 4.3.2.1).

Narratives: Appendix 3 of the ISS suggest that for accidental overdose, one subject received zolpidem ((b) (6) with TEAEs of dizziness and confusion, one subject ((b) (6) received LEM5 with a TEAE of sleep paralysis (a 1-subject increase in the LEM5 group compared to the ISS), and one subject ((b) (6) received LEM10.

Drug Abuse*:* There was no evidence of lemborexant abuse during the clinical studies. No instances of euphoria were reported as a TEAE.

Diversion*:* For the Phase 3 Pool, compliance was assessed by examination of blister packs returned to the site. Analysis of compliance showed no evidence of diversion of study drug. All individual visit records indicating that subjects had >120% compliance. Failures to return unused study drug were investigated. This occurred in three subjects in Study 303 (2 during treatment period 1; one during treatment period 2), and 13 subjects in Study 304. Most episodes were explained by loss of the study drug blister pack.

Withdrawal: At the end-of-treatment (EOT) visit, the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) was administered to assess self-reported withdrawal symptoms. An analysis of the all insomnia pool showed that cessation of lemborexant treatment did not result in withdrawal. Abrupt cessation of lemborexant did not result in rebound insomnia.

An analysis of the T-BWSQ (range 0 - 40, with higher scores indicating greater severity of withdrawal symptoms) showed no evidence of withdrawal symptoms in the LEM5 and LEM10 groups compared with PBO. Mean values at the EOS visit were similar: 1.0 for PBO, 1.2 for LEM5, and 1.1 for LEM10. Subjects in Study 303 would have been taking lemborexant for at least 6 months at the EOS visit. The number of subjects with scores ≥3 was also assessed. At the EOS visit, the incidence was 13.5% in the PBO group, 16.8% in the LEM5 group, and 13.6% in the LEM10 group. It is notable that there was no dose-response, and that the frequencies in the lemborexant groups are similar to placebo.

Rebound Insomnia: In Studies 303, 304, and 201, rebound insomnia was assessed from the subject's Sleep Diary data based on change from Screening of sSOL and sWASO during the follow-up period. There was no evidence that abrupt cessation of lemborexant caused rebound insomnia. Neither the group means nor the analyses of the proportion of subjects with rebound indicated worse sSOL or sWASO compared to pretreatment values on those parameters, according to the Applicant.

Clinical Reviewer Comments*: Nonclinical findings were less suggestive of abuse liability. However, lemborexant produces rewarding effects that are similar to the Schedule IV drug zolpidem and suvorexant in humans. Please refer to the comprehensive Controlled Substance Staff (CSS) report on Overdose, Drug Abuse Potential, Withdrawal, and Rebound for a detailed review by the Agency, located in the Action Package associated with NDA 212028. CSS suggested that lemborexant should be recommended for control under the Controlled Substances Act in Schedule IV.*

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Safety was assessed by monitoring and recording AEs, laboratory evaluations for hematology, serum chemistry, and urinalysis, periodic measurement of vital signs, weight, and ECGs, and the performance of physical examinations. Patient report of adverse events were recorded under verbatim terms. The study team examined the verbatim term and selected a representative preferred term using MedDRA standards. Adverse events were collected beginning from the time the subject signed the study informed consent form through the last study visit. Serious AEs were collected for 28 days after the last dose of study drug. Adverse events that occurred prior to the start of study drug or after the last study visit are presented in individual study case reports (CSR).

Measurements used to quantify specific aspects of safety are listed below. See Section 8.2.8 for details of their use in studies for lemborexant.

1. Postural stability: Measured as the amount of body sway via a cable placed around the subject's waist and connected to the ataxiameter.
2. Cognitive Performance: Measured using a computerized Performance Assessment Battery (PAB)
3. Objective Sleepiness: Digit Symbol Substitution Test (DSST), the Psychomotor Vigilance Test (PVT), and the Reaction Time Index (RTI)
4. Subjective Sleepiness: Karolinska Sleepiness Scale (KSS): subjective measure of sleepiness
5. Morning Sleep Propensity: Modified Multiple Sleep Latency Test (M-MSLT), measures next-morning sleep propensity
6. Middle of the Night Safety: Auditory Awakening Threshold (AAT)
7. Suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS)
8. Withdrawal Symptoms: (Tyrer Benzodiazepine Withdrawal Symptom Questionnaire, T-BWSQ)

8.2.7. Safety Analyses by Demographic Subgroups

8.2.7.1. Safety Results by Age, Sex, Race, Ethnicity, and Body Mass Index

Table 89 shows the risk of somnolence by subgroups of age, sex, race, ethnicity, and BMI. This FDA analysis was based on the adae.xpt and adsl.xpt datafiles from the 120-day safety update.

Table 89: Treatment-emergent Somnolence by Subgroup in Studies 303 and 304

		Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years
Overall		158.6	**6.3**	340.2	**19.4**	315.2	**31.4**
Age	**less than 65**	110.1	**6.4**	239.7	**20.0**	222.2	**27.5**
	over 65	48.4	**6.2**	100.4	**17.9**	93.0	**40.9**
Sex	**M**	48.4	**2.1**	108.2	**15.7**	93.6	**39.5**
	F	110.2	**8.2**	232.0	**21.1**	221.5	**28.0**
Race	**Asian**	26.7	**0.0**	63.8	**14.1**	60.8	**23.0**
	Black	13.9	**21.6**	29.0	**17.3**	24.5	**28.5**
	Other	2.1	**48.8**	2.9	**68.2**	4.3	**92.7**
	White	115.9	**5.2**	244.4	**20.5**	225.5	**32.8**
Ethnicity	**Hispanic/Latino**	16.3	**6.2**	24.6	**24.4**	20.7	**29.0**
	Not Hispanic/Latino	142.3	**6.3**	315.6	**19.0**	294.5	**31.6**
BMI	**less than 25**	60.9	**3.3**	142.4	**16.9**	117.6	**26.4**
	25-30	56.4	**5.3**	120.8	**27.3**	118.8	**39.6**
	over 30	41.2	**12.1**	77.0	**11.7**	78.8	**26.7**

Source: Reviewer-generated table using Applicant's phase 3 database.

As noted previously, somnolence shows a striking dose-response overall, with a high rate (31 events per 100 patient-years) in patients who received 10 mg lemborexant. At the 10-mg dose, the rate is particularly high in patients over the age of 65 (41 events per 100 patient-years) and in patients with race=other. (There is minimal exposure in the latter subgroup, such that confidence in the estimate is low.) The risk appears to be higher in females than males in patients who received 5 mg; however, the trend is reversed at the higher 10-mg dose. In short, sex differences are not interpretable. The label will note the increased risk of somnolence in elderly patients.

Table 90 shows treatment-emergent parasomnia by subgroups based on age, sex, race, ethnicity, and BMI. Parasomnia appears to be dose-related. Although the numbers of events are small, there is no evidence of a subgroup(s) at particular risk.

Table 91 shows treatment-emergent nausea or vomiting by subgroup. There is little evidence of a dose-response; however, females and older patients appear to be at higher risk.

Table 90: Treatment-emergent Parasomnia by Subgroup in Studies 303 and 304

		Placebo		Lemborexant 5 mg		Lemborexant 10 mg	
		Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years
Overall		158.6	**0.0**	340.2	**3.2**	315.2	**5.4**
Age	less than 65	110.1	**0.0**	239.7	**3.3**	222.2	**5.9**
	over 65	48.4	**0.0**	100.4	**3.0**	93.0	**4.3**
Sex	M	48.4	**0.0**	108.2	**2.8**	93.6	**4.3**
	F	110.2	**0.0**	232.0	**3.4**	221.5	**5.9**
Race	Asian	26.7	**0.0**	63.8	**6.3**	60.8	**6.6**
	Black	13.9	**0.0**	29.0	**3.5**	24.5	**0.0**
	Other	2.1	**0.0**	2.9	**0.0**	4.3	**0.0**
	White	115.9	**0.0**	244.4	**2.5**	225.5	**5.8**
Ethnicity	Hispanic/Latino	16.3	**0.0**	24.6	**0.0**	20.7	**4.8**
	Not Hispanic/Latino	142.3	**0.0**	315.6	**3.5**	294.5	**5.4**
BMI	less than 25	60.9	**0.0**	142.4	**4.2**	117.6	**7.7**
	25-30	56.4	**0.0**	120.8	**2.5**	118.8	**5.1**
	over 30	41.2	**0.0**	77.0	**2.6**	78.8	**2.5**

Source: Reviewer-generated table using Applicant's phase 3 database

Table 91: Treatment-emergent Nausea/Vomiting by Subgroup in Studies 303 and 304

		Placebo		Lemborexant 5 mg		Lemborexant 10 mg	
		Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years	Treatment Duration (patient-years)	Events per 100 patient-years
Overall		158.6	**3.8**	340.2	**6.5**	315.2	**6.7**
Age	less than 65	110.1	**3.6**	239.7	**6.3**	222.2	**5.0**
	over 65	48.4	**4.1**	100.4	**7.0**	93.0	**10.8**
Sex	M	48.4	**2.1**	108.2	**3.7**	93.6	**5.3**
	F	110.2	**4.5**	232.0	**7.8**	221.5	**7.2**
Race	Asian	26.7	**7.5**	63.8	**4.7**	60.8	**3.3**
	Black	13.9	**7.2**	29.0	**3.5**	24.5	**4.1**
	Other	2.1	**0.0**	2.9	**0.0**	4.3	**0.0**
	White	115.9	**2.6**	244.4	**7.4**	225.5	**8.0**
Ethnicity	Hispanic/Latino	16.3	**0.0**	24.6	**8.1**	20.7	**0.0**
	Not Hispanic/Latino	142.3	**4.2**	315.6	**6.3**	294.5	**7.1**
BMI	less than 25	60.9	**3.3**	142.4	**6.3**	117.6	**6.0**
	25-30	56.4	**3.5**	120.8	**6.6**	118.8	**5.1**
	over 30	41.2	**4.9**	77.0	**6.5**	78.8	**10.2**

Source: Reviewer-generated table using Applicant's phase 3 database

8.2.8. Specific Safety Studies/Clinical Trials

The safety and tolerability of lemborexant as reported in phase 1 studies are described below as relevant and in Section 6 (Studies 001A, 001B, 002, 003, 004, 005, 007, 008, 009, and 012). The Applicant tested the safety of lemborexant in several special populations. A study of drug liking in recreational sedative abusers (Study 103) is reviewed in Section 8.2.8, and a lemborexant driving safety was performed (Study 106; see Section 6.3.2.4 and 14.4.3 for review). A study in Alzheimer's Dementia (Study 202) is ongoing and part of a separate drug development program for the treatment of ISWRD. Safety studies including subjects with mild obstructive sleep apnea (Study 102), stable mild to moderate hepatic impairment (Study 104), stable severe renal impairment (Study 105) are reviewed below and also discussed in Section 6.3.

Respiratory Safety
Study 102 examined respiratory safety in healthy volunteers and in patients with mild OSA.

Thirty-eight (38) subjects with mild OSA, age 18 to 90, with a SpO2 ≥94% and apnea-hypopnea index <15 events per hour of sleep were studied. Subjects were exposed to LEM10 and PBO for 8 days and PSG was completed at days 1 and 8. Mean SpO2 was 94.5 on PBO and 94.5 on LEM10 on Day 1, and 94.5 PBO and 94.7 LEM10 on Day 8. There were no clinically meaningful differences between placebo and LEM10 on AHI or SpO2 at Day 1 or Day 8 between LEM10 and PBO.

SpO2 was measured as a mean percent of total sleep time (TST) during which SpO2 was <90%, <85%, and <80%. In subjects with mild OSA, there were no significant differences for LEM10 compared to PBO for any defined SpO2 threshold on Day 1 or Day 8. The highest mean percent SpO2 below a threshold was on Day 1, where SpO2 <90% for 1.04% of TST on PBO, and 1.36% of TST on LEM10.

In healthy subjects, there was an increase in the percentage of TST during which SpO2 was <90% in patients who received lemborexant. Specifically, the mean percentage (95% CI) for placebo was 0.04% (-0.12, 0.20), LEM10 was 0.16% (0.001, 0.32), and LEM25 was 0.18% (0.03, 0.34). Although these percentages are nominally statistically significantly higher than placebo, the overall percentage of TST is not likely to be clinically meaningful. For example, the upper bound of the 95% CI for LEM10, 0.32%, represents ~1.5 minutes over the course of an 8-hour night of sleep where SpO2 fell below 90%. There were no meaningful differences for SpO2 <85% or <80%.

Additionally, per the Applicant, the significant finding appeared to be related to a subject who was apparently normal at screening by AHI, but subsequently was found to have severe OSA in each treatment period (including placebo). It is more likely that this subject's OSA was missed at screening than that the subject suddenly developed severe OSA during the study.

There were no significant breathing-related adverse events in the lemborexant study group compared to placebo. However, there was one serious adverse event of COPD. Subject (b) (6) was a 66 year-old white male in the LEM10 group of Study 303. On study day 71, the patient presented with dyspnea, low appetite, diaphoresis, chills, cough, and low back pain and was hospitalized with COPD. Chest X-ray showed large hypoxic-ischemic lesions and fibro-nodular opacities; biopsy was negative. The subject was re-hospitalized on study day 291 with acute myocardial infarction. There was no additional mention of medical treatment for this subject. See *Serious Adverse Events*, Section 8.2.4.2 for more details on subject (b) (6)

Clinical Reviewer Comments: *Lemborexant was not studied in patients with moderate to severe sleep apnea or COPD. Clinically meaningful respiratory effects of lemborexant in moderate to severe obstructive sleep apnea, COPD, and possibly other groups, cannot be ruled out based on the current studies. A postmarketing requirement is necessary to examine respiratory safety of lemborexant in indivduals with COPD or moderate to severe OSA.*

Safety and Renal Impairment
Study 105 examined the safety of lemborexant in subjects with renal impairment. The study included of 16 subjects (8 with stable severe renal impairment; 8 matched healthy controls) who each received a single dose of LEM10.

In total, 5 (63%) subjects in the severe renal impairment group and 7 (88%) healthy subjects reported at least one TEAE during the study. Severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73m^2) increased lemborexant exposure (AUC) 1.5-fold but had no effect on C_{max}. Given this combination, dose adjustment is not required in patients with renal impairment. See Section 6.3.2.2. for additional details of Study 105.

Two serious adverse events were reported that fall under the SOC Renal and urinary disorders: cystitis and nephrolithiasis. In the phase 3 pool, urinary tract infections were the sixth most frequent treatment-emergent adverse event (1.8% for LEM5, 3.8% for LEM10, 1.7% for placebo). No animal data suggested drug-induced changes in the renal system.

In total, no pattern of safety concerns was identified individuals with severe renal impairment.

Hepatic Safety and Hepatic Impairment
The effect of lemborexant on patients with hepatic impairment was evaluated in Study 104. For this study, 24 subjects were randomized (8 with mild hepatic impairment, 8 with moderate hepatic impairment, and 8 matched healthy controls), and each received a single dose of LEM10. Seven (88%) subjects with mild hepatic impairment and six (75%) subjects with moderate hepatic impairment reported at least one TEAE during the study.

Table 91 shows the frequency of somnolence by group. Results do not show a discernable pattern for safety concerns.

Table 91: Incidence of Somnolence by Group in Study 104

	Child Pugh Class A (mild) (n=8) n (%)	Child Pugh Class B (moderate) (n=8) n (%)	Healthy Control Subjects (n=8) n (%)
Somnolence	7 (87.5)	5 (62.5)	7 (87.5)

Source: Modified from Applicant's Study 104 Study Report, Table 12

Clinical Reviewer Comments: *Section 8.2.4.6 on laboratory findings did not suggest an effect of lemborexant on hepatic enzymes and no Hy's Law cases were found. In study 104, lemborexant exposure (AUC and C_{max}) and terminal half-life were increased in patients with moderate hepatic impairment (Child-Pugh class B), suggesting that dosage adjustment may be necessary to avoid the increase effect of adverse events. There is no apparent relationship between hepatic impairment and the incidence of somnolence with lemborexant; however, the study was small and did not include patients with severe hepatic impairment. The label will reflect these concerns.*

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Refer to Section 5 for animal data on carcinogenicity and tumor development. The Applicant did not study carcinogenicity or tumor development in humans and no signal has been found in the existing safety data.

Human Reproduction and Pregnancy

Refer to the separate report on Reproductive and Developmental Toxicology in Section 5.5.4. Given the limited amount of data, three separate postmarketing requirements have been provided to the Applicant. See Section 13.1 for details.

Pediatrics and Assessment of Effects on Growth

The study drug has not been tested in human children. Refer to Section 5 for review of animal data.

Dose-related: As described above, the incidence of somnolence appears to be dose-related.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Lemborexant has never been marketed in the US or foreign countries.

Expectations on Safety in the Postmarket Setting

The Applicant submitted sufficient safety information to characterize adequately lemborexant's safety profile to support the initial regulatory approval decision. However, as with most clinical

trials to support regulatory submissions, the lemborexant trials had eligibility criteria that would have likely excluded many patients who could be prescribed lemborexant in clinical practice. It is possible that patients with more medical comorbidities or concomitant medication use will experience adverse reactions to a greater extent than observed in the development program. Because there were a small number of cases of parasomnias, such as complex sleep behaviors, in the development program, the incidence with 'real-world' use may differ from that observed in clinical trials. Off-label use of higher than indicated doses may be expected to result in a higher incidence of somnolence due to the observed dose-dependency of effects. Higher doses of lemborexant may also increase abuse liability, as suggested by the abuse potential study.

8.2.11. Integrated Assessment of Safety

Lemborexant is a new molecular entity (NME) with no prior approval in the US or elsewhere. The only other drug in its class is suvorexant, which received FDA approval in 2015. As such, the Applicant conducted numerous studies specifically focused on evaluating potential safety concerns with this drug, as described in this review. The overall exposure meets the ICH E1A recommendation for the extent of population exposure to evaluate the safety of drugs intended for the long-term treatment of non-life-threatening diseases. There were no deaths reported during the drug development program.

Overall, lemborexant appears to be well-tolerated in most subjects. Somnolence was the most commonly reported adverse event associated with lemborexant, and its incidence appears to be related to dose. Somnolence was the most common reason for discontinuation from clinical studies. No clinically meaningful effects on next day residual impairment were apparent. Although there were no mean differences in driving performance in subjects receiving lemborexant vs. placebo, there were a small number of performance outliers who received lemborexant 10 mg, suggesting that some individuals may experience driving impairment. Middle of the night safety assessment suggested that lemborexant may impair middle of the night memory, attention, and postural sway. Getting out of bed is common overnight, especially for the elderly; as such, the middle of the night findings may be particularly noteworthy in this population. Other common adverse events included headache and nightmares/abnormal dreams.

Other rare (<1%) but potentially clinically significant adverse reactions included sleep paralysis, hypnagogic hallucinations, falls, and cataplexy-like symptoms. Two complex sleep behavior events were reported, but there were no potentially dangerous reports of complex sleep disorders (e.g., driving). There were no reports of suicidal behavior or self-injurious behavior. Rates of suicidal ideation and endorsing wish to die were not meaningfully different than placebo.

Studies in special populations suggest no meaningful safety signal for patients with severe renal impairment. However, subjects with moderate hepatic impairment have higher exposure to lemborexant that is significant enough to warrant dosage restriction to 5 mg. In general, no dose adjustment is necessary in patients based on age, gender, race or renal impairment,

although caution should be exercised when prescribing doses higher than 5 mg to patients >65 years of age due to increased somnolence.

One area of uncertainty is respiratory safety. There were no clinically meaningful differences in overnight oxygen desaturation in individuals with mild OSA taking lemborexant compared to placebo. However, there were small dose-dependent differences in the rates of oxygen desaturation <90% in healthy patients receiving LEM10 (and LEM25) compared to placebo. COPD and moderate to severe OSA were not evaluated in the development program. Therefore, although there does not appear to be a clinically meaningful effect of lemborexant on the respiratory system, the current studies have limitations and a respiratory safety study is being issued as a post-marketing requirement to the Applicant.

The safety of lemborexant in pediatric patients, pregnant patients, and lactating women has not been established. Post-marketing studies are being required to characterize the safety of lemborexant in settings of pregnancy and lactation. No pediatric postmarketing studies are being required because of methodological issues including challenges in defining an appropriate pediatric insomnia population and assessing treatment effects in a population for which overnight polysomnography may not be practical.

In summary, the safety findings in the lemborexant insomnia development program appear generally consistent with the existing FDA-approved orexin receptor antagonist. The primary concern is somnolence and likely consequences of somnolence (e.g., middle-of-the-night impairments in attention, memory, and postural sway). Given the range of findings, product labeling should inform clinicians and patients about the potential for somnolence and related impairments, as well as other potential safety signals identified earlier in this section.

8.3.Statistical Issues

Refer to Section 8.1 for a report on statistical approach. Concerns include the limitations of interpreting findings associated with exploratory endpoints, small subgroups, and pooling data of different study durations and randomization ratios. However these concerns are consistent with many drug development programs. No specific statistical issues were identified that influence the overall conclusions of benefit-risk assessment for lemborexant.

8.4.Conclusions and Recommendations

Evidence of lemborexant's effectiveness as a treatment for insomnia disorder was assessed in two adequate and well-controlled, Studies 303 and 304. The primary efficacy endpoint in these studies was change from baseline subjective sleep onset latency (sSOL) for 303 and sleep efficiency (SE) for 304. Both studies demonstrated clinically and statistically significant changes from baseline in all primary and secondary measures, demonstrating both subjective (sleep diary) and objective (PSG) measures of clinical improvement at LEM5 and LEM10.

The Applicant submitted sufficient information to assess lemborexant's safety profile adequately. Overall, lemborexant appeared reasonably well-tolerated. The Agency's main concerns are somnolence, middle of the night safety, next-day impairment, and adverse reactions that may be related to middle of the night safety and next-day impairment. These concerns were expected based on findings in other hypnotic drugs, including the other orexin receptor antagonist. Patients will need to weigh the risks and benefits of lemborexant prior to starting treatment. Patient selection, monitoring, and dosage adjustment are strategies that can be used to minimize potential adverse reactions for lemborexant in the treatment of insomnia disorder. Lemborexant is not recommended in individuals with severe hepatic impairment, and has not been studied in individuals with moderate to severe OSA or COPD. The recommended dose is 5 mg once nightly, which may be increased based on clinical response and tolerability. However, doses higher than 5 mg in patients ≥65 years old were associated with an increased risk of somnolence.

The risk of parasomnias is present, but small and unpredictable. Cataplexy, falls, and fractures are potential safety concerns. The Agency believes these risks, and other more minor potential risks, can be addressed through labeling modifications.

Considering the prevalence of chronic insomnia in the US, limited availability of long-term pharmacotherapy for insomnia disorder, and the risks and benefits of lemborexant, the review team recommends approval. We do not believe that additional studies are needed prior to marketing to further characterize safety concerns. Postmarketing requirements will address gaps in drug-drug interaction data, pregnancy and lactation data, and the lack of data in patients with COPD and moderate to severe OSA.

Refer to Section 1.3 for a more detailed overview of the Benefit-Risk Assessment for lemborexant in the treatment of insomnia.

9. Advisory Committee Meeting and Other External Consultations

The Division did not identify questions or concerns requiring discussion by external consultants, the Psychopharmacologic Drugs Advisory Committee, or the Drug Safety and Risk Management Advisory Committee.

10. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on January 16, 2015, with a request for a full waiver from the requirements of the Pediatric Research Equity Act (PREA). The Division of Psychiatry Products (DPP) confirmed agreement with the Applicant's iPSP on April 1, 2015 on the grounds that pediatric studies are impossible or highly impracticable due to challenges in defining a homogenous pediatric insomnia population. A full waiver of pediatric studies is granted with this approval.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The table below summarizes high-level, significant changes to the proposed prescribing information made by FDA.

Section	Proposed Labeling	Approved Labeling
1. Indications and Usage	"DAYVIGO is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)	(b) (4)
2. Dosage and Administration	Dosing, preparation and administration language was provided. Use with alcohol and food effect provided.	This language was edited to clarify dosing instructions and recommendations for concomitant use with CYP3A inhibitors or inducers (in alignment with Section 7 Drug Interactions). Dosing recommendations in patients with moderate vs. severe hepatic impairment was added.
3. Dosage Forms and Strengths	Language provided	Language provided was simplified.

4. Contraindications	(b) (4)	
5. Warnings and Precautions	(b) (4)	This section was revised according to class labeling considerations (hypnotic drugs; orexin receptor antagonists) and findings from the clinical review. 5.1 CNS Depressant Effects and Daytime Impairment 5.2 Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms 5.3 Complex Sleep Behaviors 5.4 Patients with Comprised Respiratory Function 5.5 Worsening of Depression/Suicidal Ideation 5.6 Need to Evaluate for Co-Morbid Diagnoses
6. Adverse Reactions	Somnolence was presented as the most common adverse reaction. Sleep paralysis was presented under Other Adverse Reactions. (b) (4)	The table of adverse reactions was revised by the Applicant by request of the Division to include only the first 30 days of Studies 303 and 304. (b) (4) The most common adverse events leading to discontinuation of treatment were presented as somnolence, nightmares, and palpitations. Hypnagogic hallucinations and complex sleep behaviors were added to the Other Adverse

		Reactions section.
7. Drug Interactions	This language was provided.	The language in the provided table simplified and updated according to current labeling standards.
8. Use in Specific Populations	Pregnancy, lactation, reproductive, pediatric use, geriatric use, renal and hepatic impairment were discussed.	The language was simplified and updated according to current labeling standards. A pregnancy exposure registry was added. The Geriatric Use section was revised to discuss the greater incidence of somnolence with DAYVIGO 10 mg in patients ≥65 years than in patients <65 years of age. Although there is no dose adjustment required for patients with renal impairment, Section 8.6 notes that exposure (AUC) was increased in patients with severe renal impairment and patients with severe renal impairment may experience an increased risk of somnolence. Section 8.7 discusses dosage recommendations and precautions for patients with hepatic impairment. Section 8.8 notes that DAYVIGO has not been studied in patients with moderate to severe OSA or COPD and that clinically meaningful respiratory effects cannot be excluded.
9. Drug Abuse and Dependence	Language provided	Controlled substance schedule pending review by DEA
10. Overdosage	Language provided	Language revised; lemborexant is highly protein-bound and hemodialysis is not expected to contribute to elimination of lemborexant
11. Description	(b) (4)	Language provided was simplified according to current labeling practices.
12. Clinical Pharmacology	12.1 Mechanism of Action (b) (4)	12.1 Mechanism of Action: "The mechanism of action in the treatment of insomnia is presumed

	(b) (4) 12.2 Pharmacodynamics: QTc language included 12.3 Pharmacokinetics: Language on absorption, distribution, elimination, Specific populations, Sex, Race, and BMI, geriatric, pediatric patients, renal and hepatic impairment, drug interactions, and in vitro studies were provided. Figure on drug interactions provided.	to be through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive." 12.2 Pharmacodynamics: Section revised to present IC50 values for OX1R and OX2R receptors for lemborexant and its major metabolite M10. Cardiac electrophysiology section revised in accordance with QT-IRT review. 12.3 Pharmacokinetics: Language was edited for clarity. Sponsor requested to add language on the volume of distribution. Information was added on effect of food, hepatic impairment, and drug interaction studies. Drug-drug interaction study figures revised.
13. Nonclinical Toxicology	Language provided.	Language provided was simplified as per current labeling practices.
14. Clinical Studies	The overview of the clinical development program was provided. Primary and secondary endpoint results (b) (4) were displayed in a table. (b) (4) Special safety study summaries provided for effects on driving, next-day postural stability (b) (4)	This section was edited for clarity. The number of tables (b) (4) : one for Study 303 and one for Study 304. (b) (4) the pre-specified primary and secondary endpoints (with appropriate controls for type I error) were included in the tables. Tables revised in accordance with current labeling practices. (b) (4)

	(b) (4) (b) (4) withdrawal effects, respiratory safety. (b) (4)	(b) (4) The sentence "The effects of DAYVIGO at the beginning of treatment were generally consistent with later time points," was added based on clinical review of efficacy data from time points earlier than the pre-specified primary and secondary endpoints in the pivotal studies (i.e., Week 1 in Study 303 and Days 1 and 2 in Study 304). Although the results from the earlier time points in Studies 303 and 304 were not supported by pre-specified tests in the statistical analysis plan, they were adequate to support the "generally consistent with later time points" statement without any numerical data. This sentence was included to inform prescribers that clinical benefit should be anticipated earlier in the course of treatment. Section 14.2 (Special Safety Studies) revised to present results from studies assessing middle of the night safety, effects on next-day postural stability and memory, effects on driving, rebound insomnia, and withdrawal effects. The Effects on Driving section was updated in accordance with current labeling practices and includes the statement that driving ability was impaired in some subjects taking 10 mg DAYVIGO and that patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment. (b) (4)

		(b) (4)
16. How Supplied/ Storage and Handling	Language provided.	Language provided was simplified according to current labeling practices.
17. Patient Counseling	Language provided on administration, daytime impairment, use with alcohol and other drugs, tolerance, abuse, dependence	Language updated to reflect changes in other sections of Full Prescribing Information.
Medication Guide	Language provided	Medication guide updated to reflect changes in other sections of Full Prescribing Information. Consultative input received from the patient labeling team and incorporated as appropriate.

12. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues necessitating a REMS have been identified.

13. Postmarketing Requirements and Commitment

13.1. Postmarketing Requirements

After completing the safety and efficacy review for lemborexant for the treatment of insomnia, the following postmarketing requirements (PMRs) were issued to the Applicant:

13.1.1. Maternal, Fetal, and Infant Outcomes of Women Exposed to Lemborexant

The DPMH review team is requiring that the Applicant conduct three post-marketing studies.

- A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lemborexant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. The goal of this study is to evaluate the long-term safety of lemborexant in women exposed during pregnancy, including assessing risks of pregnancy complications and adverse effects on the developing fetus and neonate. Data are needed on the safety of lemborexant use during pregnancy.

- A pregnancy study that uses a different design from the pregnancy registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess for major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to lemborexant during pregnancy compared to an unexposed control population. The goal of this study is to evaluate the long-term safety of lemborexant in women exposed during pregnancy, including assessing risks of pregnancy complications and adverse effects on the developing fetus and neonate. Data are needed on the safety of lemborexant use during pregnancy.

- A lactation study in women who are receiving therapeutic doses of lemborexant, to assess concentrations of lemborexant in breast milk using a validated assay and to assess the potential for adverse effects on the breastfed infant. The study is necessary because there are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data in women who are breastfeeding precludes characterizing the potential risks to an infant during lactation, including whether they experience adverse reactions such as sedation.

13.1.2. Clinical PMR to Assess Respiratory Safety

The Applicant will be required to conduct one randomized, double-blind, placebo-controlled study to evaluate the short-term respiratory safety of lemborexant (DAYVIGO) in subjects with moderate to severe obstructive sleep apnea (OSA) and in subjects with moderate to severe chronic obstructive pulmonary disease (COPD).

Applicants seeking indications for the treatment of insomnia disorder frequently include studies evaluating respiratory safety because many hypnotic drugs have been associated with respiratory depression. Accordingly, the labels for most hypnotic drugs include a consideration related to the respiratory system under Warnings & Precautions (e.g., respiratory depression for AMBIEN CR, compromised respiratory function for BELSOMRA, and severe sleep apnea for ROZEREM). As such, adequate respiratory safety studies are expected for new drug development programs for insomnia disorder, such a lemborexant.

The PMR was requested for two reasons. First, the drug development program for lemborexant only assessed respiratory safety in healthy subjects and those with mild OSA and thus lacks data for moderate to severe OSA/COPD populations who might be more susceptible to treatment emergent respiratory depression. Second, a respiratory safety signal of potential concern was identified in healthy individuals who were given single doses of lemborexant: the percentage of time in which peripheral capillary oxygen saturation decreased below 90% during the night was numerically higher for lemborexant than placebo, and this effect appeared to be dose-dependent. Although the numerical difference was modest in healthy subjects and would not be expected to have any clinical implications, a PMR related to respiratory safety in patients with more severe respiratory disease (e.g., moderate to severe OSA and COPD) is warranted for lemborexant.

The results of the PMR will help determine if there is an effect of lemborexant on respiratory safety in individuals with moderate to severe OSA and moderate to severe COPD, which will inform product labeling. Additional studies in OSA are important because the estimated prevalence of OSA in the general population is high, ranging from 9% to 38% [35], and approximately 40% of patients with OSA report difficulty with sleep maintenance and symptoms of insomnia disorder [36]. As such, the effect of hypnotic drugs on respiratory safety is an important clinical consideration for individuals with OSA as well as other respiratory disorders such as COPD.

13.1.3. Clinical Pharmacology PMCs

The clinical pharmacology review team requested that the Applicant conduct two drug-drug interaction (DDI) studies. The following studies should be designed and conducted in accordance with the FDA Guidance for Industry entitled “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies.”

- An in vitro DDI study to assess the potential of lemborexant and its metabolites as an inducer for CYP2C8, CYP2C9 and CYP2C19. Lemborexant and its metabolites (M4, M9 and M10) have modest induction effects on CYP3A4 in vitro in human hepatocytes. Because both CYP3A4/5 and CYP2C enzymes are induced via activation of the pregnane X receptor, the clinical pharmacology reviewers recommended further evaluation of the potential of lemborexant and its metabolites to induce CYP2C8, CYP2C9 and CYP2C19.

- An in vitro DDI study to assess the potential of lemborexant as a P-glycoprotein (P-gp) substrate at clinically relevant concentrations. The reason for this request is because lemborexant was determined to be a poor substrate of P-gp at higher than clinically relevant concentration (3 µM). The in vitro testing concentration of 3 µM for lemborexant is 300-fold higher than clinically relevant concentration (unbound C_{max}: 10 nM). At high concentrations, there is a potential for P-gp been saturated and the reported efflux ratio may have been underestimated. Thus, the clinical pharmacology reviewers recommend re-conducting an in vitro DDI study to assess the potential of lemborexant as a substrate for P-gp substrate at clinically relevant concentrations.

14. Appendices

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14.2. Financial Disclosure

The Applicant submitted forms for the following covered clinical studies: Study 201, Study 303, and Study 304. There were no disclosures in Study 201 or Study 303.

Covered Clinical Study (Name and/or Number): 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 119		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None listed		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 201 Eisai

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 23		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): None listed		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 88		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 119		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Table 92: Exposure Ratios of M10 in Animals Compared to Humans

Species	Dose	$AUC_{(0-24)}$ of M10 (ng·h/mL)		Animal to Human Exposure Ratio of M10[a]		Remarks
		Male	Female	Male	Female	
Human	10 mg/man	259±110		—	—	Proposed MRHD
Mouse[b]	100 mg/kg	2000	3700	7.72	14.3	–
	300 mg/kg	4630	6300	17.9	24.3	HD in carcinogenicity study was 500 mg/kg
	1000 mg/kg	8830	12,700	34.1	49.0	HD in 4-week study
Rat	10 mg/kg	ND	1.76	ND	0.007	–
	30 mg/kg	9.85	ND	0.04	ND	NOAEL (female) in 13-/26-week study
	100 mg/kg	74.1	204	0.29	0.79	NOAEL (male) in 13-/26-week study HD in carcinogenicity study was 300 mg/kg
	1000 mg/kg	259	3070	1.00	11.9	HD in 13-/26-week study and pre-EFD study
Monkey	10 mg/kg	353	320	1.36	1.24	NOAEL in 39-week study
	100 mg/kg	3650	3210	14.1	12.4	–
	1000 mg/kg	2820	6780	10.9	26.2	HD in 39-week study

$AUC_{(0-24)}$ = AUC from zero to 24 hours, HD = high dose, MRHD = maximum recommended human dose, ND = no data, NOAEL = no observed adverse effect level.
a: Human, mice, rat, and monkey plasma samples from the human multiple ascending dose study (Study No. E2006-A001-002), the mouse 4-week study (Study No. DMPKT2014-007), the rat 4-week study (Study No. ES15364), and the monkey 4-week study (Study No. ES15365), respectively, were used to determine exposure ratios.
b: The study (Study No. DMPKT2014-007) was considered exploratory (non-GLP) and the methods used for the measurement of M10 in mice were qualified but not fully validated.
Sources: Study Nos. DMPKT2014-007 (mouse), ES15364 (rat), and ES15365 (monkey).

Source: Applicant's table; Toxicology Written Summary NDA 212028

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.4.1. Population Pharmacokinetic Analysis

Objective

The objectives of the population PK analysis were to:

- Describe the PK of lemborexant in healthy adult and elderly subjects, and in subjects with insomnia disorder.
- Assess the effects of intrinsic (e.g., body weight, age, sex, BMI, race) and extrinsic factors (e.g., formulation, food intake, drug-drug interactions (DDIs) such as concomitant moderate cytochrome P450 3A (CYP3A) inhibitors and proton pump

inhibitors (PPI)) on lemborexant PK, focusing on key parameters of apparent clearance (intrinsic and extrinsic factors) and volume of distribution (intrinsic factors only).

Analysis dataset

Subjects included in the population PK analysis were healthy subjects or subjects with insomnia disorder from phase 1 studies and subjects with chronic insomnia or insomnia disorder in Study E2006-G000-201 (Study 201), Study 303, and Study 304. Subjects included in the PK analysis had received at least one dose of lemborexant and had at least one lemborexant concentration measurement for which reliable dosing and sampling history was available.

The final PK dataset included 12230 observations from 1892 subjects. For Study 303, 2211 lemborexant plasma concentrations were available from 726 subjects, aged 18 to 85 years. For Study 304, 1972 lemborexant plasma concentrations were available from 524 subjects, aged 55 to 88 years. Other studies contributed 8047 observations from 642 subjects, of which phase 1 studies contributed 6543 observations from 407 subjects. Summaries of the demographic and physiological covariate information are summarized below.

Table 93: Summary of Baseline Covariates

	All Subjects (N=1892)		
Covariate (unit)	**Mean (SD)**	**Median**	**Range (Min-Max)**
Age (years)	55 (14.1)	57	18-88
Weight (kg)	75.5 (15.7)	74.1	37-168
BMI (kg/m^2)	27.0 (5.0)	26.5	14.4-62.1
Bilirubin (µmol/L)**	6.9 (4.1)	6.0	1.7-42.9
Albumin (mg/dl) *	44.2 (2.8)	44	26-53
Alanine transaminase (IU/L)*	20 (11.9)	17	5-178
Aspartate transaminase (IU/L)*	20.7 (8.3)	19	8-194
Alkaline phosphatase (IU/L)	72.9 (22.0)	71	13-256
Creatinine Clearance (mL/min)*,[a]	101.7 (35.1)	97.3	26.8-319
Dose	Range: 1 – 100 mg***		
Sex	Females = 1249; Males = 643		
Race	White = 1334; Black/African-American = 335; Asian/other Asian (excluding Chinese and Japanese) = 32; Japanese = 155; Chinese=5, American Indian/Alaskan/Other/Missing=31		
Formulation	Tablet=1755, Capsule=137		
Concomitant PPI	Yes=112, No=1780		
Concomitant moderate CYP3A inhibitors	Yes=22, No=1870		

[a] capped at 150 mL/min when evaluated as a covariate; *N=1891; **N=1888; ***Data from dose 200 mg was excluded from the PK analysis as it was causing model instability.

Abbreviations: IU, international units; SD, standard deviation; PK, pharmacokinetics; PPI, patient package insert
Source: Page 8 in cpms-e2006-004r-v1.pdf

Methodology

Structural (fixed effects) compartmental modeling of lemborexant pharmacokinetics was informed by extensively sampled Phase I data. These data initially informed the absorption and disposition features of the compartmental model. Extensively sampled data also informed the residual error model. Due to the generally sparse, steady-state pharmacokinetic data available from phase 2/3 studies in insomnia subjects; it was deemed appropriate to only consider covariates on the aspects of the model describing oral clearance. All covariates were introduced

into the model under univariate analysis based on visual inspection of the plots for Eta(CL/F) vs continuous and categorical covariates. Each significant covariate from the univariate analysis at p≤0.01 were carried forward in the model and removed in the backward elimination step if the p values were < 0.001.

Results

The estimates of pharmacokinetic parameters from the final population pharmacokinetic model are provided in Table 94.

Table 94: Final Population PK Parameter Estimates of Lemborexant – All Data

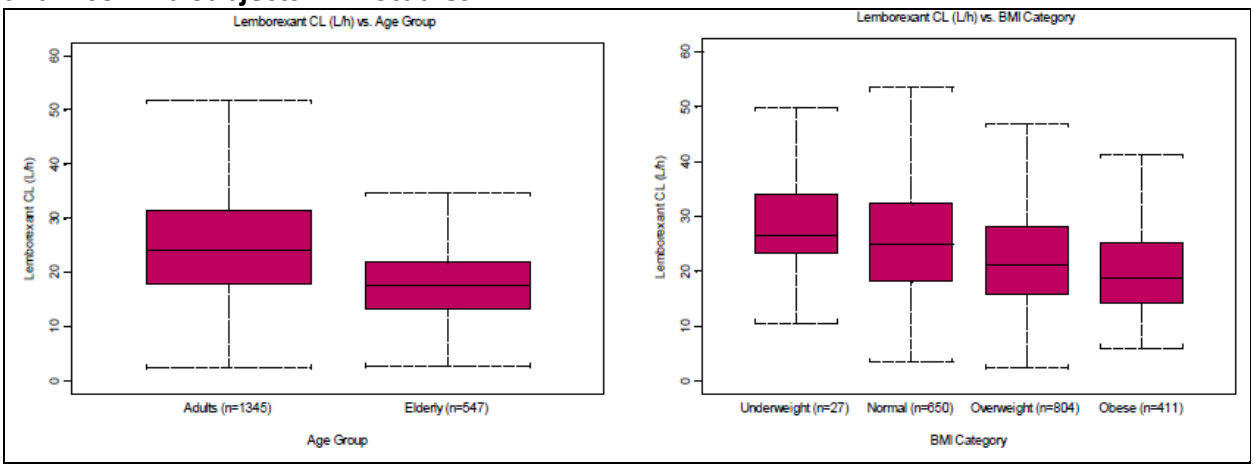
	NONMEM Estimate		
Parameter	**Point Estimate**	**%RSE**	**95% CI**
Apparent clearance: CL/F			
Basal CL/F (L/h)	22.7	0.252	22.6 - 22.8
Effect of BMI on CL/F (exponent)	*-0.428*	*12.9*	*-0.536 - -0.320*
Effect of ALP on CL/F (exponent)	*-0.118*	*21.3*	*-0.167 - -0.0688*
Effect of Elderly on CL/F (ratio)	*0.739*	*0.307*	*0.735 – 0.753*
Apparent central volume of distribution: V2/F			
Basal V2/F (L)	9.09	0.0909	9.07 - 9.11
Inter-compartmental clearance: Q3/F			
Basal Q3/F (L/h)	32.1	0.0417	32.1 - 32.1
Apparent first peripheral volume of distribution: V3/F			
Basal V3/F (L)	278	0.0156	278 - 278
Inter-compartmental Clearance: Q4/F			
Basal Q4/F (L/h)	31.0	0.0997	30.9 - 31.1
Apparent second peripheral volume of distribution: V4/F			
Basal V4/F (L)	783	0.0815	782 - 784
Duration of Absorption :D1			
D1 for capsule (h)	0.467	Fixed	
D1 tablet effect (ratio)	*0.254*	*Fixed*	
D1 bedtime dosing effect (ratio)	*2.33*	*Fixed*	
First-order absorption rate constant: Ka (1/h)			
Ka for capsule (1/h)	0.532	Fixed	
Ka tablet effect (ratio)	*1.12*	*Fixed*	
Ka food intake effect (ratio)	*0.695*	*Fixed*	
Absorption lag time: ALAG1			
ALAG1 (h)	0.403	Fixed	
F1			
F1 fed	1.21	Fixed	
Inter-individual variability(%CV)			
CL/F	48.1	3.68	
V2/F	142	23.2	
Q3/F	56.8	17.2	
V3/F	82.0	15.0	
Q4/F	46.5	11.4	
V4/F	41.4	10.5	
D1	167	Fixed	
Ka	43.8	Fixed	
F1	68.1	Fixed	
Residual variability			
Proportional (TAD > 3h; %CV)	14.3	1.07	
Additive (TAD > 3h; ng/mL)	0.0189	21.2	
Proportional (TAD ≤ 3h; %CV)	32.9	1.19	
Additive (TAD ≤ 3h; ng/mL)	2.62	3.15	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL/F = apparent clearance; V2/F = apparent central volume of distribution; Q/F=inter-compartment clearance; Ka = first order absorption rate constant; V3/F = apparent first peripheral volume of distribution; V4/F = apparent second peripheral volume of distribution; ALAG1 = lag time in absorption; L = liter; h = hour; WGT = body weight; CI = confidence interval; %CV = Square root of variance *100.

Source: Table 10 on Page 61 in cpms-e2006-004r-v1.pdf

Model-predicted clearance estimates by age and BMI category are shown in Figure 53.

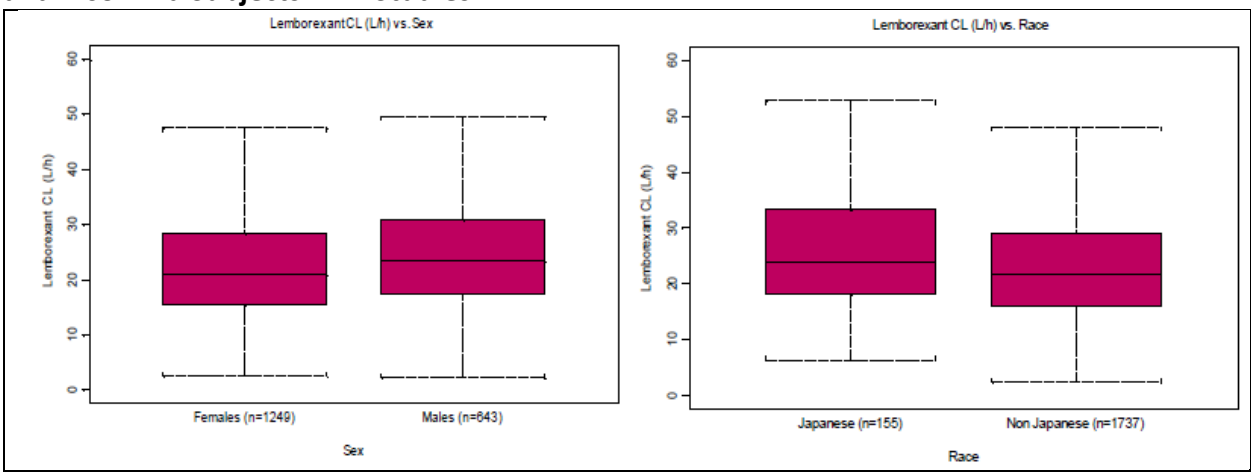
Figure 53: Model-Predicted Lemborexant CL/F vs. Age Group and vs. BMI Category in Healthy and Insomnia Subjects – All Studies



Abbreviations: BMI, body mass index; CL/F, apparent total clearance of the drug from plasma after oral administration
Source: Page10 on in cpms-e2006-004r-v1.pdf

Model-predicted clearance estimates by gender and race category are shown in Figure 54.

Figure 54: Model-Predicted Lemborexant CL/F vs. Age Group and vs. BMI Category in Healthy and Insomnia Subjects – All Studies



Abbreviations: BMI, body mass index; CL/F, apparent total clearance of the drug from plasma after oral administration
Source: Page10 on in cpms-e2006-004r-v1.pdf

Using the final PK model, simulations (N=250 per subset) assessed the impact of age (elderly vs adults) and BMI category (underweight, overweight and obese vs normal) on lemborexant exposure (AUC_{ss}) following 5 mg once daily dosing to steady state. In the simulations for BMI categories, observed median BMI values from the PK dataset were used. To quantify the effect of age group on lemborexant exposure, a statistical analysis for equivalence was performed and the results are presented below.

Table 95: Summary of Statistical Analysis Comparison of Lemborexant AUC_{ss} Following Lemborexant 5 mg/Nightly in Adult and Elderly Subjects

Dose (mg)	Reference	Test	Ratio (%) (Elderly/Adults)	Lower 90% CI	Upper 90% CI
5	Adults (BMI=26.5 mg/m^2)	Elderly (BMI=26.5 mg/m^2)	139	129	150

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval
Source: Page 12 on in cpms-e2006-004r-v1.pdf

The analysis reflects lemborexant exposure to be statistically significantly higher (ratio (%) = 139; 90 % CI [129-150]) in elderly subjects compared to adults (assuming a median BMI of 26.5 kg/m^2).

To assess the range of effect of BMI category on lemborexant exposure, an equivalence assessment was performed, and results are presented below.

Table 96: Summary of Statistical Analysis Comparison of Lemborexant AUC_{ss} Following Lemborexant 5 mg/Nightly in Each BMI Category

Dose (mg)	Reference	Test	Ratio (%) (Test/Reference)	Lower 90% CI	Upper 90% CI
5	Normal (BMI=22.9 kg/m^2)	Underweight (BMI=17.4 kg/m^2)	89	83	96
5	Normal (BMI=22.9 kg/m^2)	Overweight (BMI=27.4 kg/m^2)	111	103	119
5	Normal (BMI=22.9 kg/m^2)	Obese (BMI=32.7 kg/m^2)	119	111	128

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval
Source: Page 12 on in cpms-e2006-004r-v1.pdf

The statistical analysis indicates that lemborexant exposure is similar in underweight, normal and overweight subjects. Obese subjects have a slightly higher exposure compared to subjects with normal BMI (ratio = 119, 90 % CI [111-128]).

In summary:

- Lower lemborexant clearance was observed in elderly subjects (age ≥ 65 years) compared to adults
- Higher BMI was associated with lower lemborexant clearance
- Neither race nor sex had an effect on lemborexant clearance

Overall, dose adjustments or warnings in the label are not needed based on these changes in AUC_{ss}.

The Applicant conducted three studies in special safety populations. The study designs had limitations, as described below.

Table 97: Lemborexant Studies in Special Safety Populations

Study Number	Study Design	Population	N	Limitations
E2006-A001-102	DB, PC, crossover study of respiratory safety of LEM10	Adult and elderly subjects with mild OSA Males or females ≥18 to ≤90 Years SpO2 ≥94%, OSA,	LEM10 and PBO (n=78)	Limited to Mild OSA Moderate to Severe OSA and COPD were not evaluated
E2006-A001-104	Open-label, parallel-group study of the PK of LEM10	Males or females 18 to 79 years with stable hepatic impairment (Child-Pugh classification A or B) and healthy matched control subjects	LEM10 (n=24)_	
E2006-A001-105	Open-label, parallel-group study of the PK of LEM10	Males or females 18 to 79 years with stable severe renal impairment and healthy matched control subjects	LEM10 (n=16)	

Abbreviations: DB, double blind; LEM, lemborexant; OSA, obstructive sleep apnea; PBO, placebo; PC, placebo-controlled; PK, pharmacokinetics

Respiratory Safety: As described in Section 8.2, increased desaturations on lemborexant were noted in the respiratory safety study in healthy adults, but the percentage of time was so small that it was not clinically meaningful.

Hepatic Impairment: The Applicant did not recommend dose adjustment for mild or moderate hepatic impairment, and to avoid use with severe hepatic impairment. See Section 8.2 for detailed review by the Agency. The internal clinical pharmacology review demonstrated terminal $t_{1/2}$ was prolonged 1.6-fold in patients with moderate hepatic impairment, resulting in 2-fold higher accumulation of lemborexant. In subjects with mild hepatic impairment, there is an increased risk of somnolence.

Renal Safety: Results of the renal studies demonstrated that C_{max} and AUC increased by 5 and 50% in patients with severe renal impairment. Label warning indicates the patient should be cautious about somnolence, but no other warnings were warranted per the clinical pharmacology team.

Clinical Reviewer Comments*: Given the above findings, the recommendation is as follows: With moderate hepatic impairment, the dose of lemborexant should be limited to 5 mg and added caution should be noted for the increased potential of somnolence with lemborexant. For moderate hepatic impairment, no dosage adjustment is needed; however, there is caution for the increased potential of somnolence with lemborexant. Lemborexant should be avoided in patients with severe hepatic impairment.*

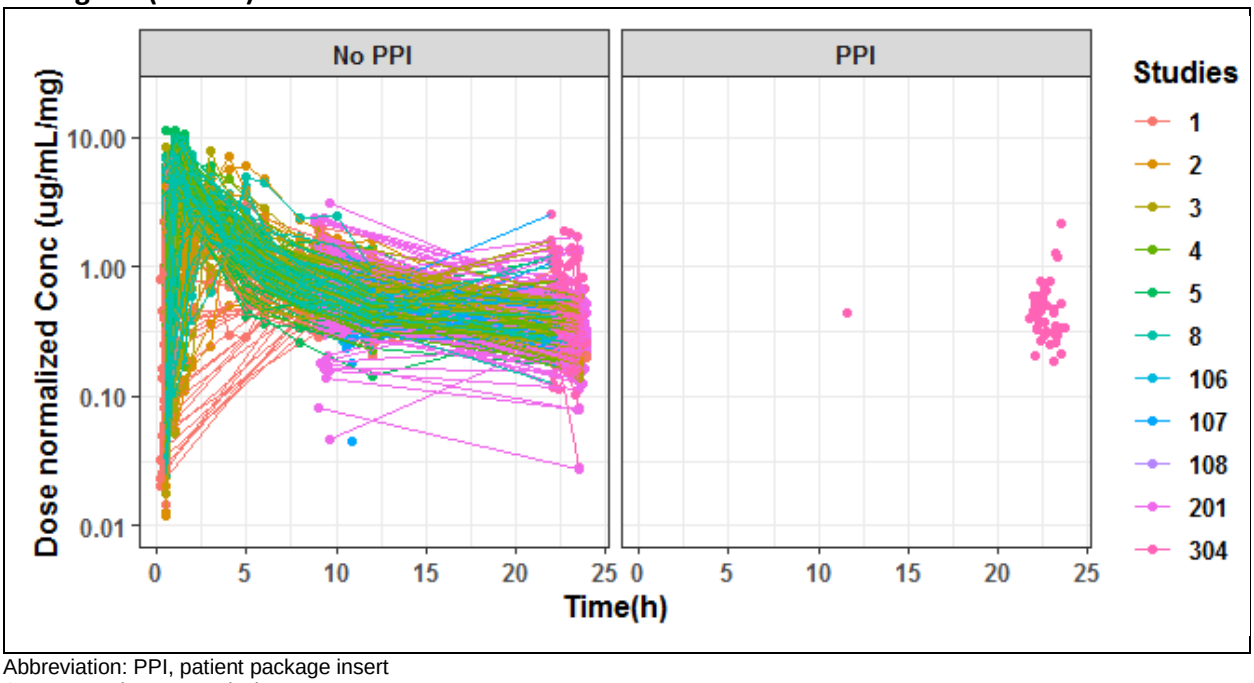
Sex, Race, and BMI
No effect of sex or racial groups was noted. Based on a population pharmacokinetic analysis of patients receiving 5 or 10 mg lemborexant once daily, the BMI effect on apparent clearance was minor and was not considered clinically relevant.

Geriatric Patients
Based on a population pharmacokinetic analysis of patients receiving 5 or 10 mg lemborexant once daily, apparent clearance was 26% lower in elderly (>65 years of age). However, this effect was not clinically relevant.

Reviewer Comments: *The Applicant's analysis and labeling language are acceptable.*

Additionally, the Applicant evaluated the influence of concomitant proton pump inhibitors (PPI) on the pharmacokinetics of lemborexant. Figure 55 shows dose-normalized lemborexant concentrations versus time in subjects taking lemborexant with and without PPIs.

Figure 55: Dose Normalized Lemborexant Concentrations in Subject Taking PPI and Not Taking PPI (No PPI)



Abbreviation: PPI, patient package insert
Source: Reviewer's analysis

Reviewer Comments: *The highlighted sentences above are not acceptable* (b) (4)

14.4.2. Physiologically based Pharmacokinetic (PBPK) Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report (cmps-e2006-pbpk) titled "Development of a Physiologically-Based Pharmacokinetic Model for lemborexant and Simulations of Cytochrome P450-Mediated Drug-Drug Interactions" to assess the effect of a weak CYP3A4 inhibitor on the pharmacokinetics (PK) of lemborexant.

The Division of Pharmacometrics has reviewed the original PBPK report, the addendum to the report, supporting modeling files, the Applicant's response to FDA request for information dated May 31, 2019, July 19, 2019, and July 31, 2019, and concluded the following:

- The PBPK model of lemborexant is adequate to predict the PK of lemborexant in healthy volunteers.
- The magnitude of increase in lemborexant PK when co-administrated with a weak CYP3A inhibitor is expected less than 2-fold.

Background

Lemborexant is developed to treat insomnia and irregular sleep wake rhythm disorder. The recommended oral dose of lemborexant is 5 mg once daily (QD) with option to increase to 10 mg QD. The maximum recommended dose of lemborexant is 10 mg once daily. Lemborexant can be administrated with or without food; however, time to sleep onset may be delayed if taken with or soon after a meal.

Multiple formulations of lemborexant were used in the clinical PK studies. Lemborexant was administered as an oral capsule in the single and multiple ascending dose studies and human mass balance study. An immediate release (IR) tablet (the to-be-market formulation) of lemborexant was used in DDI clinical studies. Results of a relative bioavailability study (E2006-

A001-005) showed that both the rate and extent of lemborexant absorption after tablet administration are comparable to the reference capsule for all strengths tested (2.5, 10, and 25 mg).

Linear dose-exposure relationships were clinically observed following a single dose in healthy subjects in the doses ranging from 2.5 to 75 mg. Similar trend was reported after multiple dose administration. Following a single dose administration, median T_{max} was 1 to 1.5 hours in the 1-, 2.5-, 5-, and 10-mg dose groups and up to 3 hours in the 100 mg and 200 mg dose groups (Study E2006-A001-001) and the effective half-life was 17 and 19 hours after multiple doses of 5 and 10 mg (Study E2006-A001-002). Human mass-balance study (E2006-A001-007) reported approximately 13% of total oral dose was excreted unchanged in feces. Minimal unchanged drug was detected in urine (<1%). Lemborexant accounted for 26.5% of total drug-related exposure while its metabolites M10, M9, M4, and M18 accounted for 12.5%, 6.6%, 6.3%, and 6.0%, respectively. Of note, these metabolites were not incorporated into the lemborexant PBPK model. An oral clearance (CL/F) of 32.8 L/h for lemborexant following single oral administration of 10 mg capsule was reported in the human mass-balance study (E2006-A001-007).

In vitro studies showed that the plasma protein binding values of lemborexant were 87.4% to 88.7% in humans. Recombinant cytochrome (CYP) assay and hepatocyte metabolism studies suggested that there is no non-microsomal metabolism and CYP3A4/5- mediated oxidation was the main clearance pathway for lemborexant (Applicant's Clinical Pharmacokinetic Summary sec 2.6.4.5.4). In vitro study showed that lemborexant was a poor substrate for P-glycoprotein (P-gp), but its metabolites M4, M9, M10 were substrates of P-gp. Lemborexant and its metabolites were not substrates of cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP1B) 1/3.

Lemborexant is a reversible inhibitor for CYP2A6 with an IC50 value of 7.8 µmol/L. The IC50 values for the other CYP isoforms were estimated similar (CYP2C19) or greater than 30 µmol/L. Lemborexant and its metabolites M4, M9, and M10 induce CYP2B6 and CYP3A mRNA levels greater than 2-fold. Applicant conducted clinical DDI studies with a CYP2B6 substrate (bupropion) and CYP3A substrates (midazolam and Loestrin 1.5/30 (an oral contraceptive containing norethindrone [NE] 1.5 mg and ethinyl estradiol [EE] 0.03 mg). Clinical DDI studies showed that lemborexant is a weak CYP2B6 inducer as it decreases 45.5% of S-bupropion AUC and 24% of [S,S]-hydroxylated bupropion AUC. Lemborexant did not have a clinically significant effect on midazolam exposure (less than 15% increase from the baseline).

In vitro, with the exception of OAT1, lemborexant inhibited all investigated transporters (P-gp, BCRP, BSEP, MATE1, MATE2-K, OATP1B1, OATP1B3, OAT3, OCT1, and OCT2) with IC50 values of 7.4 to 32.2 µmol/L. Applicant stated the DDI inhibition potential of lemborexant on transporters are low as the steady-state C_{max} for lemborexant following 10 mg is approximately 0.1 µM and $C_{max,u}$ is estimated around 0.01 µM (Applicant's Clinical Pharmacokinetic Summary Table 2.7.2-3).

The Applicant conducted clinical drug-drug interaction (DDI) studies in healthy subjects to assess DDI potential of lemborexant as a CYP3A substrate and an inducer modulator for CYP3A and CYP2B6 pathways. Table 98 summarizes the ratios of the observed maximum plasma concentration (C_{max}) and plasma AUC of substrates in the presence and absence of a perpetrator in these studies.

Table 98: Clinical DDI Effects of Lemborexant as a CYP3A Substrate or As an Inducer for CYP3A or CYP2B6 Pathway

Substrate	Perpetrator	Treatment	Substrate's C_{max} ratio	Substrate's AUC ratio
Lemborexant	Itraconazole	Itraconazole 200 mg QD for 20 days + lemborexant 10 mg SD on Day 8	1.36	3.61
Lemborexant	Fluconazole	Fluconazole 400 mg on day 1 followed by 200 mg QD for 14 days + lemborexant 10 mg SD on Day 5	1.62	3.75
Lemborexant	Rifampin	Rifampin 600 mg QD for 20 days + lemborexant 10 mg SD on Day 8	0.08	0.03
Lemborexant	Famotidine	Famotidine 40 mg SD + lemborexant 10 mg SD	0.73	1.00
Midazolam	Lemborexant	Lemborexant 10 mg for 17 days + Midazolam 2mg SD on day 10	1.13	1.13
Contraceptive (Loestrin, NE 1.5 mg+ EE 0.03 mg)	Lemborexant	Lemborexant 10 mg for 14 days + Loestrin SD on day 15	1.0 (NE)/ 1.0 (EE)	0.95 (NE)/ 1.1(EE)
Bupropion	Lemborexant	Lemborexant 10 mg for 17 days + bupropion 75 mg+ SD on day 10	0.50	0.54

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; DDI, drug–drug interaction; EE, ethinyl estradiol; NE, norethindrone; QD, once daily; SD, single dose
Source: Applicant's Summary of Clinical Pharmacology Studies Table 2.7.2-8, 9, 10, 11, 13, 14, 15. C_{max} and AUC ratio values are geometric means. Ratios were expressed as with modulator/without modulator.

In its proposed USPI, the Applicant recommended that lemborexant should not be concomitantly administered with moderate and strong CYP3A inhibitors, and CYP3A inducers. The proposed recommended dose is 5 mg for coadministration with a weak CYP3A inhibitor based on PBPK analyses.

Methods

PBPK MODEL STRUCTURES AND DEVELOPMENT

The PBPK model of lemborexant was developed based on in vitro, physicochemical properties, human ADME study (E2006-A001-007) and clinical PK data. Briefly, an Advanced Dissolution, Absorption and Metabolism model and a full body PBPK model was used to describe the distribution and PK of lemborexant. The tissue/plasma partition coefficient (Kp) was estimated using the method2 in Simcyp. A Kp scalar value of 0.51 was selected by fitting to the plasma concentration data in human mass balance study. The unbound fraction of lemborexant in

plasma was 0.11, and the blood to plasma concentration ratio was 0.636 (Applicant's Clinical Pharmacokinetic Summary section 2.7.2.1.1).

The effective membrane permeability in humans (Peff) of lemborexant was predicted based on physicochemical properties using the Mechanistic Peff model in Simcyp. The predicted Peff was 8.799×10^{-4} cm/s. Applicant selected the 'solution' formulation in their PBPK model for the capsule formulation. For the tablet formulation, the in-vitro dissolution profile collected for the 10 mg IR tablets in pH 1.2 and 6.8 buffer was used as model inputs for simulations in the fasted and fed states, respectively.

In vitro studies indicated that lemborexant metabolism is mediated predominantly by CYP3A and non-CYP enzymes are not involved in lemborexant metabolism. The Applicant assumed a 100% contribution of CYP3A pathway to the total hepatic clearance (fm_{CYP3A} value = 1) in the model. Applicant applied the retrograde method to calculate Clint(s) using the observed oral clearance (CL/F) of 32.8 L/h reported in human mass-balance study. The hepatic intrinsic clearance (CLuH,int) value of 0.463 µL/min/pmole) was applied in the model.

Simulations were performed using the default healthy volunteer population model (software's library, V17). Six perpetrators' PBPK models from SimCYP built-in library including clarithromycin, erythromycin, fluconazole, fluoxetine, fluvoxamine, verapamil, and rifampin were used in the PBPK simulations for the respective DDIs.

The Applicant used the itraconazole (ITZ) and OH-itraconazole (OH-ITZ) models developed by [37] which were different from the SimCYP library models in many parameters, such as logP, pKa, Fa, Ka, Vss, CYP3A4 clearance parameters (Vmax, Km), Peff (for itraconazole), and CYP3A4 Ki (for OH-itraconazole). The Applicant stated that Chen's model (referred as IQ-WG ITZ model) has been verified with itraconazole and OH-itraconazole plasma concentration-time profiles observed following single and multiple dose administration of itraconazole, and 20 clinical ITZ DDI studies [37].

PBPK MODEL VERIFICATION

The performance of PBPK model to predict the PK profile of lemborexant after single and multiple dose administration in healthy volunteers was evaluated by comparing the simulated and observed clinical PK data (studies E2006-A001 and 002). The fm_{CYP3A} of lemborexant was verified against the DDI study with itraconazole and fluconazole (study E2006-A004). The PBPK simulations and respective study designs conducted for lemborexant model development, verification and application are listed in Table 99.

Table 99: PBPK Simulations and Study Design Used for Lemborexant Model

#	Study	lemborexant Dosing Regimen	Perpetrator/ Victim	Dosing Regimen	Simulation Duration	PBPK Model Objective
1	001	2.5, 10, 100 mg SD capsule formulation	NA	NA	10 days	Development
2	001	10 mg SD IR formulation	NA	NA	10 days	Development
3	002	10 mg QD capsule formulation	NA	NA	10 days	Verification
4	004	10 mg SD on Day 7	Itraconazole	200 mg QD for 20 days	21 days	Verification
5	004	10 mg SD on Day 7	Rifampin	600 mg QD for 20 days	21 days	Verification
6	004	10 mg SD on Day 5	Fluconazole	400 mg loading and 200 mg QD for 16 days	17 days	Verification
7	NA	10 mg SD on Day 8	Verapamil	80 mg q8h for 20 days	21 days	Application
8	NA	10 mg SD on Day 8	Erythromycin	500 mg q6h for 20 days	21 days	Application
9	NA	10 mg SD on Day 8	Fluvoxamine	50 mg QD for 20 days	21 days	Application
10	NA	10 mg SD on Day 25	Fluoxetine	40 mg QD for 39 days	40 days	Application

Abbreviations: IR, immediate release; NA, not applicable; PBPK, physiologically based pharmacokinetic; QD, once daily; SD, single dose
Note: Applicant selected the 'solution' formulation in the PBPK model for the capsule formulation
Source: Applicant simulation outputs, Reviewer's analysis

Reviewer Comments: *Although the lemborexant model was not verified with PK data following multiple-dose administration of the IR tablets, it is acceptable because the model predicts the PK profiles after single and multiple oral dose of lemborexant for the capsule formulation (Study E2006-A001-001, 002)*. In addition, the clinical relative bioavailability study (Study E2006-A001-005) indicates that both the rate and extent of lemborexant absorption after tablet administration are comparable to the reference capsule for all strengths tested. Differences between the tablet and capsule formulations in $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ across all dose levels were each less than 13%. Differences between the tablet and capsule formulations in C_{max} across all dose levels were each less than 16%. A trend of a 30-minute delay in median Tmax for the capsule formulation was only observed at higher doses. Dissolution profiles of IR tablets were used for simulations in fasted and fed states to assess the food effect. The model underestimates the observed C_{max} but was able to capture the ratios of C_{max} and AUC between fasted and fed conditions (data not shown). As all the clinical PK and DDI studies relevant to the objective of this review were all in fasted condition, the applicability of the current lemborexant PBPK for food effect was not reviewed. PBPK modeling to evaluate the effect of elevated gastric pH on the lemborexant PK also was also not reviewed since there was a dedicated DDI study with famotidine (an antacid) (Table 98).

PBPK MODEL APPLICATION

The verified PBPK model of lemborexant was applied to predict the following:

- the effects of clarithromycin (strong CYP3A inhibitor), erythromycin (moderate CYP3A inhibitor); fluvoxamine (moderate CYP3A4 inhibitor) and verapamil (moderate CYP3A4 inhibitor and P-gp inhibitor) on the PK of lemborexant;
- the effect of fluoxetine on the PK of lemborexant;
- the effect of ranitidine (developed as a weak CYP3A inhibitor) on the PK of lemborexant.

Results

Evaluation of the Applicant's lemborexant PBPK model for DDI potential assessment

The Applicant's lemborexant PBPK models was able to describe lemborexant PK following a single and multiple dose of lemborexant. The comparison of the predicted and the observed PK are shown in Table 100 and Figure 56.

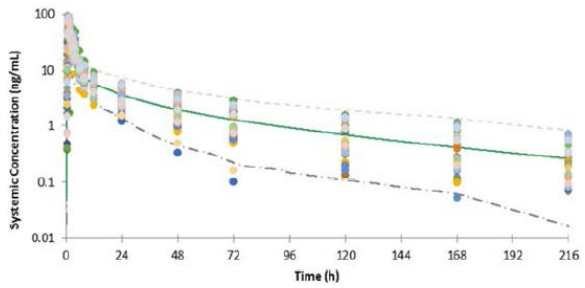
Table 100: Comparison of PBPK Predicted and Observed Mean C_{max} and AUC Values of Lemborexant

	Observed			Predicted			Pred./Obs	
lemborexant Dosing Regimen	C_{max} (ng/mL)	T_{max} (h)	AUC (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng.hr/mL)	C_{max}	AUC
2.5 mg SD (Solution)	14.9	1.01	74.4	6.79	1.06	66.4	0.46	0.89
10 mg SD (Solution)	32	1	274	27.1	1.06	354	0.85	1.29
100 mg SD (Solution)	242	3	4300	261	1.08	3270	1.08	0.76
10 mg SD (IR tablet)	54.3	1	411	25.3	1.06	327	0.47	0.80
10 mg QD (Solution) (Day 14)	44.8	1.75	321	32.9	1.1	327	0.73	1.02

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; IR, immediate release; PBPK, physiologically based pharmacokinetic; QD, repeated once-daily dose; SD, single dose; T_{max}, time to maximum plasma concentration
Note: C_{max} and $AUC_{(0-t)}$ values are expressed as geometric mean, and T_{max} values are expressed as median. AUC_{inf} for SD, $AUC_{24h,ss}$ for QD.
Source: Applicant's PBPK report Table 6-8, Reviewer simulation

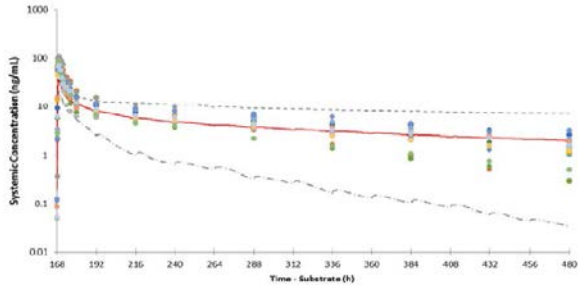
Figure 56: Predicted and Observed Plasma Concentration-Time Profiles of Lemborexant

1) 10 mg SD, IR, Study 001



Source: Figure 5 in Applicant's PBPK report (solid line represents the mean simulated data, dot- and dot-dash line represent the 95th and 5th percentile of the simulated data)

2) 10 mg SD + itraconazole , Study 004



Source: Figure 8 in Applicant's PBPK report (solid line represents the mean simulated data, dot- and dot-dash line represent the 95th and 5th percentile of the simulated data)

Abbreviations: IR, immediate release; SD, single dose; PBPK, physiologically based pharmacokinetic

The proposed fm_{CYP3A} value of 1 was verified by comparing the predicted and observed lemborexant PK parameters with and without CYP3A modulators (itraconazole, fluconazole and rifampin). As shown in Table 101, although the model was able to describe the observed AUC ratios with itraconazole and fluconazole, the model significantly under-estimated the effect with rifampin. The metabolism rationale for such under-prediction is unknown as the in-vitro study suggested that lemborexant is nearly completely metabolized via CYP3A and P-gp mediated clearance is not clinically significant. Due to the significant underestimation, the model is inadequate to predict DDI effects of a CYP3A inducer on the lemborexant exposure.

Table 101: Observed and PBPK Predicted C_{max} and AUC Ratios for Lemborexant in the Presence of CYP3A4 Modulators

Concomitant Drug and Dose	**C_{max} Ratio(s)**			**AUC Ratio(s)**		
	Observed (GM)	Predicted (GM, 90% CI)	Pred/obs	Observed (GM, CV%)	Predicted (GM, 90% CI)	Pred/obs
Itraconazole 200 mg QD	1.36	1.39 [1.32, 1.42]	1.02	3.58 (32%)	3.11 [2.93, 3.31]	0.87
Fluconazole 200 mg QD	1.32	1.37 [1.35, 1.40]	1.03	3.76 (15%)	2.83 [2.73, 2.93]	0.75
Rifampicin 600 mg QD	0.085	0.38 [0.35, 0.42]	**4.47**	0.033 (49%)	0.19 [0.17, 0.21]	**5.75**
Clarithromycin 500 mg BID		1.48 [1.44, 1.52]			4.87 [4.35, 5.52]	
Verapamil 80 mg q8h		1.43 [1.39, 1.47]			3.87 [3.53, 4.23]	
Erythromycin 500 mg q6h		1.46 [1.42, 1.50]			4.33 [3.97, 4.73]	
Fluvoxamine 50 mg QD		1.06 [1.01, 1.11]			1.09 [1.08, 1.09]	
Fluoxetine 40 mg QD		1.21 [1.19, 1.23]			1.77 [1.68, 1.85]	

Abbreviations: BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GM, geometric mean; PBPK, physiologically based pharmacokinetic; QD, once daily; AUC, area under the curve
Note: Geometric mean and CV shown for observed PKGeometric mean with [5, 95] percentile shown for predicted PK
Geometric mean with [5, 95] percentile shown for predicted PK

Evaluating the Applicant's itraconazole model

An information request was sent to request detail model verifications of the Applicant's itraconazole model in terms of the ability to 1) describe itraconazole and OH-ITZ PK following administration of itraconazole capsules under the fasted and fed conditions, and 2) predict clinical DDI effects of itraconazole capsules administrated in the fasted condition. The Applicant submitted a summary of verification in both the fed and fasted conditions.

Applicant confirmed that the model used in the submitted PBPK analysis was the same as that described in [37] (referred as IQ-WG ITZ model). Different fa and ka values were used in the IQ-WG ITZ model to fit to the observed PK data (Table 102).

Table 102: fa and ka Values Used in the IQ-WG ITZ PBPK Model for Different Formulations

	IQ WG ITZ		
	Solution fasted	Capsule fasted*	Capsule fed
fa	0.7	0.5	0.65
ka (1/hr)	0.45	0.2	0.25

Abbreviations: fa, fraction absorbed; ITZ, Itraconazole; IQ-WG, innovation and quality-working group; ka, disassociation constant; PBPK, physiologically based pharmacokinetic
*used in the Applicant's PBPK analysis (Applicant's information request response dated 7/31/2019)

Table 103 compared the predicted PK parameters of itraconazole and OH-ITZ using Simcyp's and the Applicant's itraconazole model following 200 mg QD in the fed or fasted condition.

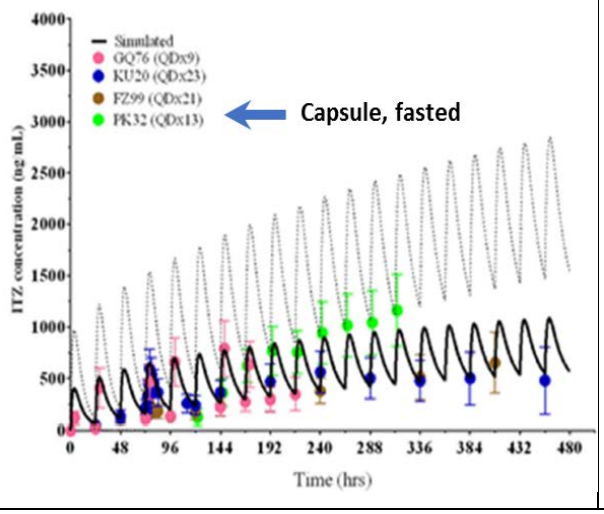
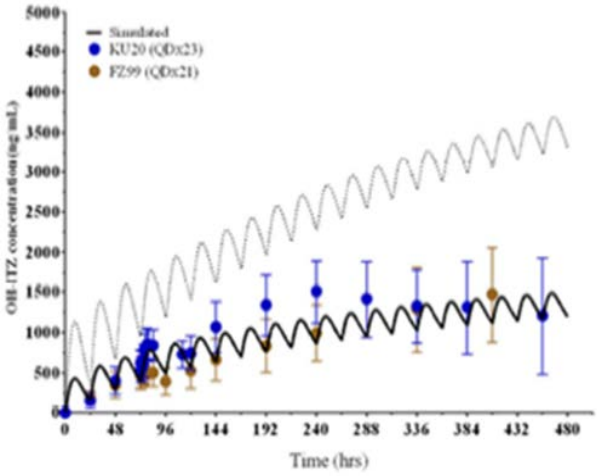
Table 103: Comparison of the Simulated PK Parameters of Itraconazole and OH-ITZ at Steady State (on Day 20) Using Simcyp's and the Applicant's Itraconazole Model

Compound	Parameter	Simcyp solution fasted*	IQ-WG solution fasted*	IQ-WG capsule fasted	IQ-WG capsule fed *
Itraconazole	C_{max} (ng/mL)	1378.21	1096.8	408.48	683.48
	AUC (ng-hr/mL)	22289.87	15421.5	6433.69	10692.14
OH-ITZ	C_{max} (ng/mL)	2040.16	1342.2	593.67	980.6
	AUC (ng-hr/mL)	41752.98	25964.1	11430.09	19197.8

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; IQ-WG, innovation and quality-working group; OH-ITZ, hydroxy-itraconazole
*Simulated by reviewer using Applicant's workspace file ('e2006-10mg-ddi-with-itra-200mg_181031') with different fa and ka values in Table 102 Simcyp version 17 was used

As shown in Figure 57 (submitted by the Applicant, same as those in [37], the IQ-WG itraconazole PBPK model reasonably described the itraconazole PK following 200 mg QD administration of itraconazole capsules in both the fed and fasted conditions. Reviewer notes that the simulations seemed to be conducted with ka and fa values in fed condition. There is no clinical PK data available for OH-ITZ in the fasted condition.

Figure 57: Simulated and Observed Itraconazole and OH-ITZ PK Profiles Following 200 mg QD Administration of Itraconazole Capsules

(a) Simulated mean (lines) and observed (solid point) plasma concentrations of ITZ	(b) Simulated mean (lines) and observed (solid point) plasma concentrations of OH-ITZ
	

Observed data are from 4 different studies where 200 mg ITZ capsules were administrated once daily, under fed or fasted condition. Only Study PK32 included ITZ PK under fasted condition. No OH-ITZ PK under fasted condition is available.

Black lines represent the simulated mean concentration and the dotted lines represent standard derivation of 100 individuals (10 trials of 10 subjects per trial) simulated.

Abbreviations: ITZ, Itraconazole; OH-ITZ, hydryxy-itraconazole; PK, pharmacokinetics; QD, once daily
Source: Figure 4 (H&I panel) of Applicant's information request response dated 5/31/2019

Table 104 presents the summary of verification for IQ-WG ITZ model by comparing the observed and simulated DDI effects of itraconazole on sensitive or moderate sensitive CYP3A substrates in the fasted condition. The model underpredicted five of six clinical DDI effects of itraconazole ranging 7 to 54%.

Table 104: Verification of IQ-WG ITZ PBPK Model With Sensitive or Moderate Sensitive CYP3A Substrates in the Fasted Condition

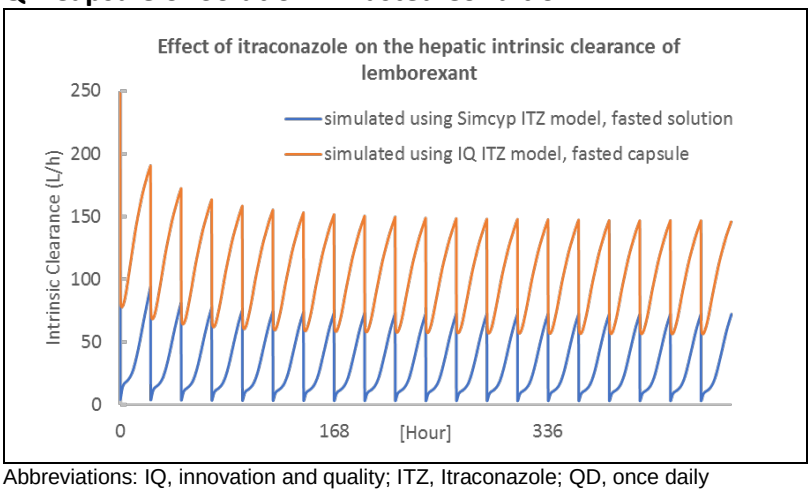
	Substrate	Clinical Itraconazole Dosing Regimen	Obs. AUC ratio	Pred. AUC ratio	Pred/Obs
[38]	Midazolam (Day 6, 2 h after ITZ)	200 mg QD capsule for 6 days, 3 hrs fasting before midazolam	6.64	5.32	0.80
[39]	Midazolam (Day 4, 1 h after ITZ)	200 mg QD capsule for 4 days, 3 hrs fasting before midazolam	10.8	5.00	0.46
[40]	Quinidine (Day 4, 1 h after ITZ dose)	200 mg QD capsule, for 4 days, (assumed fasted)	2.42	2.25	0.93
[41]	Alprazolam (Day 4, 1 h after ITZ)	200 mg QD capsule for 6 days; overnight fasting on Day 4	2.8	1.82	0.65
[42]	Midazolam (IV)(Day 4)	200 mg QD capsule for 4 days, fasted	2.78	2.44	0.88
[38]	Midazolam (IV)(Day 4), 2 h after ITZ	200 mg QD for 6 days, 3 hrs fasting before midazolam	3.23	2.51	0.78
[43]	Simvastatin (Day 4), 2 h after ITZ	200 mg QD capsule for 4 days, fasted	10	17	1.70

Abbreviations: AUC, area under the curve; ITZ, Itraconazole; IV, intravenous; QD, once daily

Formulation-depended food effects on the exposure of itraconazole has been reported [44]; [45] and led to different dosing recommendation. To reach a higher exposure, Itraconazole solution is recommended to be administrated without food (SPORANOX® solution label (NDA 020657, Reference ID: 4400952)) and capsule formulations is to be given with a full meal (SPORANOX® capsule label (NDA 020083, Reference ID: 4400948)). As shown in Table 103, the exposure of itraconazole and ITZ-OH following 200 mg capsule in fasted condition is the lowest among different DDI regimens.

A further analysis on the inhibition potential of Applicant's itraconazole model shows that the Applicant's itraconazole (200-mg capsule QD, fasted) model simulated lesser inhibition effect on the CYP3A pathway than other dosing regimens. As shown in Figure 58, the IQ-WG itraconazole model predicted to reduce the hepatic clearance of lemborexant by up to 77 % (200-mg capsule QD, fasted) compared to 98.5% (200-mg solution QD, fasted) inhibition using Simcyp’s itraconazole model.

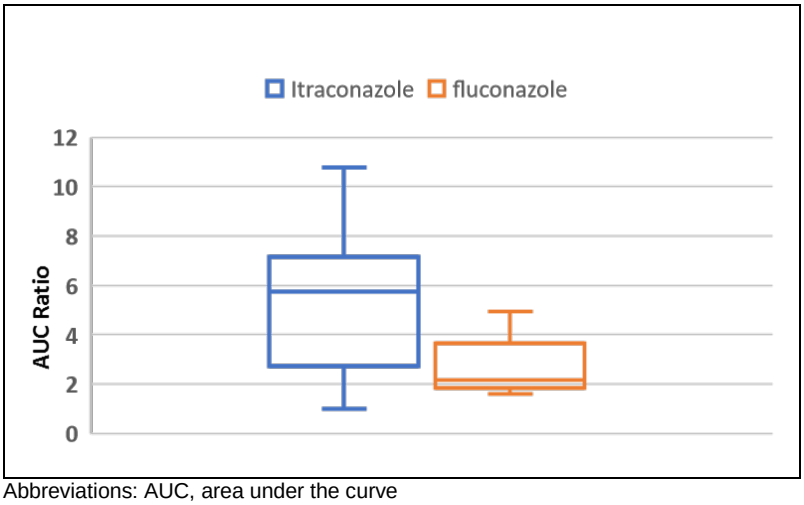
Figure 58: Comparison of the Hepatic Intrinsic Clearance of Lemborexant Following 200 mg QD Capsule or Solution in Fasted Condition



Abbreviations: IQ, innovation and quality; ITZ, Itraconazole; QD, once daily

One notable finding of the submitted clinical DDI result is that the DDI effect of itraconazole on lemborexant exposure is similar to those observed with fluconazole. Generally, one would expect stronger clinical DDI effects with itraconazole than fluconazole on the same CYP3A substrate. Based on the clinical DDI studies reported in University of Washington Metabolism and Transport Drug Interaction Database (DIDB®) (https://www.druginteractioninfo.org/), the geometric mean of AUC ratios of midazolam in the presence and absence of itraconazole (n=12) or fluconazole (n=13) were 5.0 or 2.5, respectively (as shown in Figure 59).

Figure 59: Comparison of Observed AUC Ratio of Midazolam With/Without Coadministration With Itraconazole or Fluconazole



Abbreviations: AUC, area under the curve

Many factors can influence the magnitude of inhibition effect for a single pathway. The DDI difference between a strong and moderate inhibitor might be less obvious if the fm_{CYP3A} value of the substrate is low or the substrate has a lower hepatic clearance (based on FDA in-house data analyses). Nevertheless, as the fm_{CYP3A} assigned to lemborexant in the current PBPK model

is 100%, the similar DDI effects observed with itraconazole or fluconazole could be due to the lower exposure of itraconazole and its metabolite.

Predicting DDI effect with a weak CYP3A inhibitor
Applicant proposed to avoid the use of lemborexant with a strong or moderate CYP3A inhibitor based on clinical DDI studies. For weak CYP3A inhibitors, the Applicant's proposed a dose of 5 mg lemborexant based on the simulated 77% increase in lemborexant AUC when lemborexant is co-administrated with fluoxetine (Table 101).

Fluoxetine is a CYP3A inhibitor in-vitro and decreased the exposure of alprazolam by 30% based on a clinical DDI study [46]. Alprazolam has been suggested as an index CYP3A substrate [47] but is a moderate sensitive CYP3A substrate based on the FDA DDI website (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1).

In response to FDA's information request submitted on July 19, 2019, the Applicant indicated that fluoxetine was a weak CYP3A4 inhibitor listed in the 2012 FDA DDI guidance and was recently removed from the weak CYP3A4 inhibitor list in 2017 FDA DDI guidance as neglectable DDI effects of fluoxetine on midazolam, triazolam and lovastatin were reported. To further investigate the effect of a weak CYP3A inhibitor on lemborexant PK, the Applicant submitted a ranitidine model which was developed by one of the Simcyp Consortium company members as a weak CYP3A inhibitor but not a gastric pH modulator.

For the ranitidine model, the Advanced Dissolution, Absorption and Metabolism model was used to describe absorption, a full body PBPK model was used to describe the distribution, permeability-limited model was incorporated for the liver and kidney to account for the transporters' effect. The ranitidine model was validated against PK following single oral dose of 150 mg and multiple oral doses of 150 mg twice daily ranitidine. The CYP3A4 Ki value of 12 µM was obtained by fitting against the ranitidine-midazolam DDI data [48] where ranitidine increased midazolam AUC and C_{max} by 52% and 66% respectively. The model was then validated against the ranitidine-triazolam DDI study data in the literature.

The ranitidine model was then used to predict its effect on the PK of lemborexant. The predicted geometric mean AUC ratio and C_{max} ratio of lemborexant with/without ranitidine were predicted to be about 1.58 and 1.13, respectively.

Conclusions
The Applicant's lemborexant PBPK model is sufficient provide dosing recommendation with a CYP3A inhibitor. The magnitude of increase in lemborexant PK when the drug is co-administrated with a weak CYP3A inhibitor is expected less than 2-fold.

14.4.3. Driving Study Review

Background

The next-day driving performance of healthy adults (21 to 64 years) and elderly subjects (≥65 years) was evaluated in Study E2006-E004-106 by assessment of the mean standard deviation of the lateral position (SDLP) during an on-road driving test in the morning following a single dose and multiple doses of lemborexant (2.5, 5 and 10 mg) administered at bedtime.

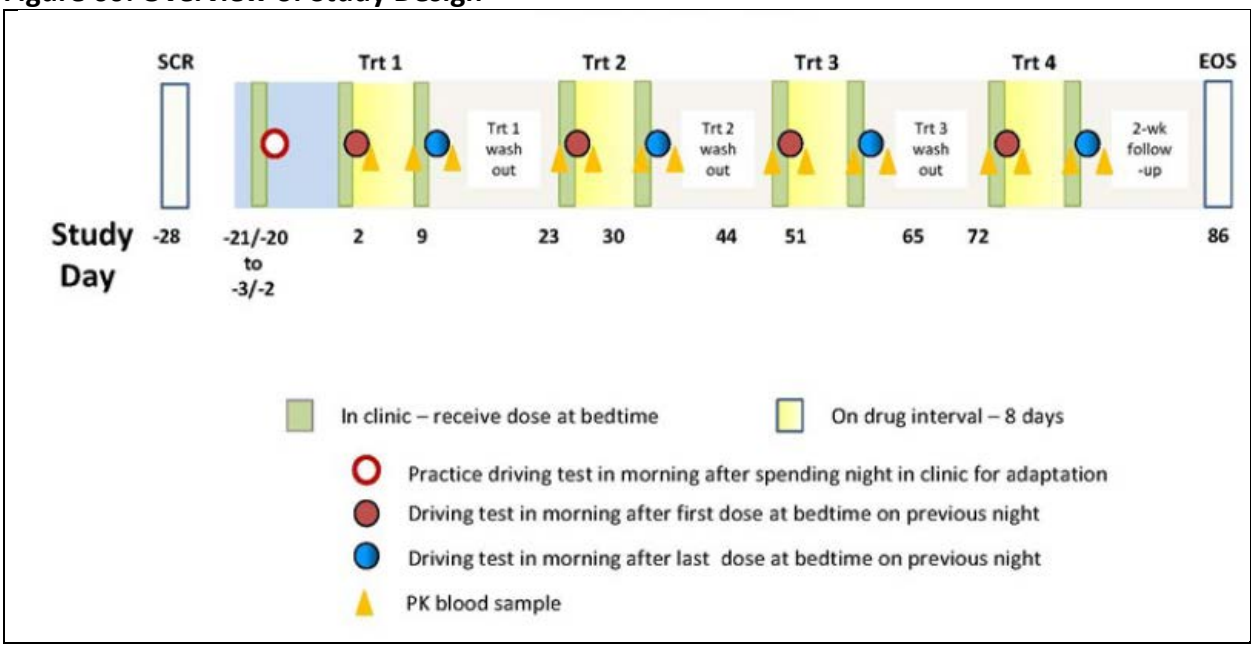
Study design

Figure 60 shows the design features of the driving study. Although there were 5 treatments, this was a 4-period, incomplete crossover design, as all subjects were to receive placebo and zopiclone but only 2 of the 3 dose levels (2.5, 5 and 10 mg) of lemborexant.

At the time of conduct of the study, the dose levels being evaluated in the phase 3 studies of lemborexant for insomnia disorder and in phase 2 for ISWRD included 2.5, 5, and 10 mg. Therefore, these dose levels were evaluated in the current study to assess the impact of single and multiple doses of lemborexant on driving performance.

Randomization was stratified by age group (adult: 21 to 64 years versus elderly: ≥65 years) in a 1:1 ratio and was balanced for sex such that there were no fewer than 10 males or 10 females per age group. Blood concentrations of lemborexant, metabolites, and S-zopiclone were measured after each driving assessment. A blood sample was also taken before the first dose at each treatment period after Treatment Period 1 to measure any residual concentrations from the previous treatment period, and before dosing when the subjects returned to the site for the second driving test of the pair at each treatment period to measure exposure after multiple doses. The on-road driving assessment was conducted in the morning after the first dose of study drug and again in the morning after subjects had taken a dose for 8 consecutive nights at bedtime. The relationship between next-day residual lemborexant concentrations (approximately 10.5 hours postdose) and driving performance was evaluated.

Figure 60: Overview of Study Design



Abbreviations: EOS, end of study; PK, pharmacokinetic; SCR, screening; Trt, treatment

Subjects operated a specially instrumented vehicle for approximately 1 hour over a 100-km (62 miles) primary highway circuit, accompanied by a licensed driving instructor who had access to dual controls (brakes and accelerator). The instructions were to drive with a steady lateral position between the delineated boundaries of the slower (right) lane, while maintaining a constant speed of 95 km/h (59 mph). Instructions were followed except to pass slower vehicles, and to leave and reenter the highway at the turnaround point. During the drive, the vehicle's speed and lateral position were continuously recorded. These signals were digitized at a rate of 4 Hz and stored on an onboard computer for later preprocessing and analysis. The primary and secondary outcome variables from the driving test were SDLP and the number of lapses.

Study Endpoints

Primary Endpoint

SDLP on the driving test on the morning following the first dose and following the last dose of lemborexant 2.5, 5, and 10 mg compared to placebo.

Secondary Endpoints

- Number of lapses on the driving test on the morning following the first dose and following the last dose of lemborexant 2.5, 5, and 10 mg compared to placebo.
- Outliers on SDLP: Number and proportion of subjects with difference in SDLP between lemborexant 2.5, 5, or 10 mg or zopiclone and placebo greater than 2.4 cm or less than -2.4 cm (symmetry analysis).
- Outliers on number of lapses: Number and proportion of subjects with difference in number of lapses between lemborexant 2.5, 5, 10 mg, or zopiclone and placebo greater

than or equal to 2. A lapse was defined as moving laterally from the chosen position in the lane by at least 100 cm for a minimum of 8 seconds.

- Other outliers: Number and proportion of subjects who never started a scheduled driving test or who stopped prematurely, regardless of SDLP difference from placebo, in lemborexant 2.5, 5, 10 mg versus zopiclone and versus placebo
- SDLP and number of lapses on the driving test on the morning following the first dose and following the last dose of lemborexant 2.5, 5, and 10 mg compared to placebo, by age group.

Pharmacokinetic/Pharmacodynamic Endpoint

- Plasma concentrations of lemborexant following the driving test and selected outcome variables from the driving test including SDLP and number of lapses.

Analysis methodology

The primary analysis on SDLP was performed using repeated-measures analyses of variance. The model included treatment, time, period, sequence, age group, and interaction between treatment and time as fixed effects, and a repeated effect for time, with subject within period. An unstructured covariance matrix was used. The least squares (LS) means, difference in LS means of each lemborexant dose compared to placebo, 95% confidence interval (CI)s and P values were calculated.

Statistical Reviewer Comments: *Reporting p-value from the primary analysis is misleading.* (b) (4) [redacted] *Comparing the upper bound of the 95%CI of the treatment difference of SDLP to a pre-defined cut point is the right way to conclude similarity with evidence. A pre-defined cut point was chosen to be 2.4 cm.*

A symmetry analysis, where the frequency and percentage of subjects who are classified as impaired, defined as the active-placebo difference in SDLP >2.4 cm (or where the driving test was stopped, regardless of SDLP) with lemborexant 2.5, 5, 10 mg, or zopiclone versus placebo, separately for the 2nd and 9th day of each treatment period, were analyzed compared to subjects classified as improved, defined as the active-placebo difference in SDLP < -2.4 cm, using the McNemar test.

Statistical Reviewer Comments: (b) (4) [redacted] *A significant p-value can support with confidence that there is a treatment difference. However, a non-significant p-value can only support that there is not enough evidence to reject the assumption of no treatment difference. The symmetry analysis is not a proper analysis for the purpose of the study.*

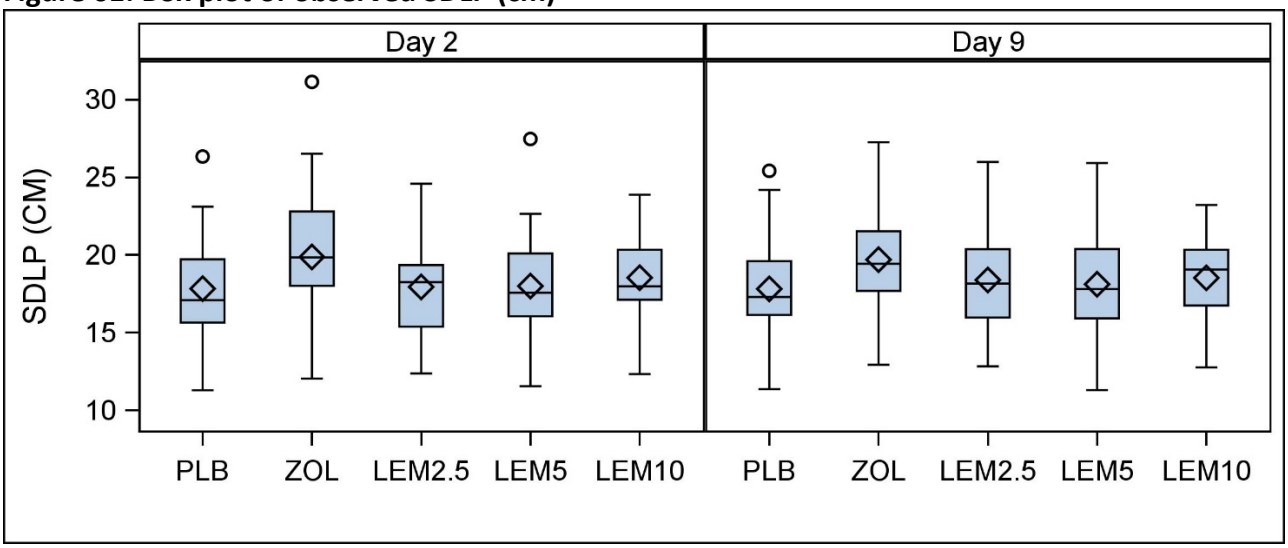
Results

Analysis for primary endpoint

For all 48 subjects, driving was assessed on both drives (Day 2 and Day 9) during all 4 Treatment Periods, even if a drive stopped early. Three drives from 2 subjects were stopped prematurely after taking zopiclone (an adult female was too sleepy while driving and stopped herself on both Day 2 and Day 9; an elderly male self-reported loss of concentration and the drive was stopped by the driving instructor on Day 9 due to the inability of the subject to maintain a consistent speed. As planned, SDLP data from the start of a drive until completion or until a drive was stopped were used in the analyses; there were no missing SDLP data. A total of 3 subjects had to repeat entire treatment periods due to mechanical issues with the car (2 subjects) or technical issues with the video recorder in the car (1 subject). The observed SDLP for each day and treatment arm is graphically presented in Figure 61. The primary analysis results on SDLP is presented in Table 105. All the upper bounds of the 95% CIs of the treatment differences of SDLP are less than 2.4 for all three lemborexant doses.

Statistical Reviewer Comments: *For those who stopped driving, using SDLP from the start of the drive until a drive was stopped may underestimates the potential SDLP. This may lead to an underestimated treatment difference. However, in the study, there were no stops during any drives after any lemborexant dose. Therefore, this concern may be dismissed.*

Figure 61: Box plot of observed SDLP (cm)



Abbreviations: LEM, lemborexant; PLB, placebo; SDLP, standard deviation of the lateral position; ZOL, zolpidem
Source: FDA statistician's analysis (adpd.xpt)

Table 105:Primary Analysis Results on SDLP (cm)

	Placebo N=48	Lemborexant 2.5 mg N=32	Lemborexant 5 mg N=32	Lemborexant 10 mg N=32
Day 2				
LS mean	17.835	17.851	18.062	18.567
SE	0.4566	0.5826	0.5826	0.5826
LS mean difference: active dose – placebo	-	0.016	0.227	0.732
CI for difference	-	(-1.444, 1.477)	(-1.234, 1.688)	(-0.729, 2.193)
P value[a]	-	0.9824	0.7594	0.3240
Day 9				
LS mean	17.818	18.299	18.181	18.559
SE	0.4437	0.5674	0.5674	0.5674
LS mean difference: active dose – placebo	-	0.480	0.362	0.741
CI for difference	-	(-0.941, 1.902)	(-1.059, 1.784)	(-0.681, 2.163)
P value[a]	-	0.5056	0.6155	0.3051

Abbreviations: CI, confidence interval; LS, least squares; p-value, probability value; SE, standard error
a: The P value is the comparison between each lemborexant dose and placebo.
Source: Sponsor's Table 11 in CSR, verified by FDA statistician

Analysis for secondary endpoint

Symmetry analysis for SDLP

The symmetry analysis compared those subjects whose SDLP improved (subjects with a change from placebo in SDLP <-2.4 cm) to those whose SDLP showed impairment (subjects with a change from placebo in SDLP >2.4 cm, or where the driving test was stopped, regardless of SDLP). As the FDA statistical reviewer pointed out in the analysis methodology, the symmetry analysis is not a proper analysis for the purpose of the study. The result of the symmetry analysis is presented below in Table 106 for the purpose of completeness only. Sponsor's reported results differ from the results below by 1 for zopiclone arm. After requiring Sponsor's code, it was found that the difference was caused by a stopped drive with SDLP < 2.4. The Applicant failed to classify the subject as impaired.

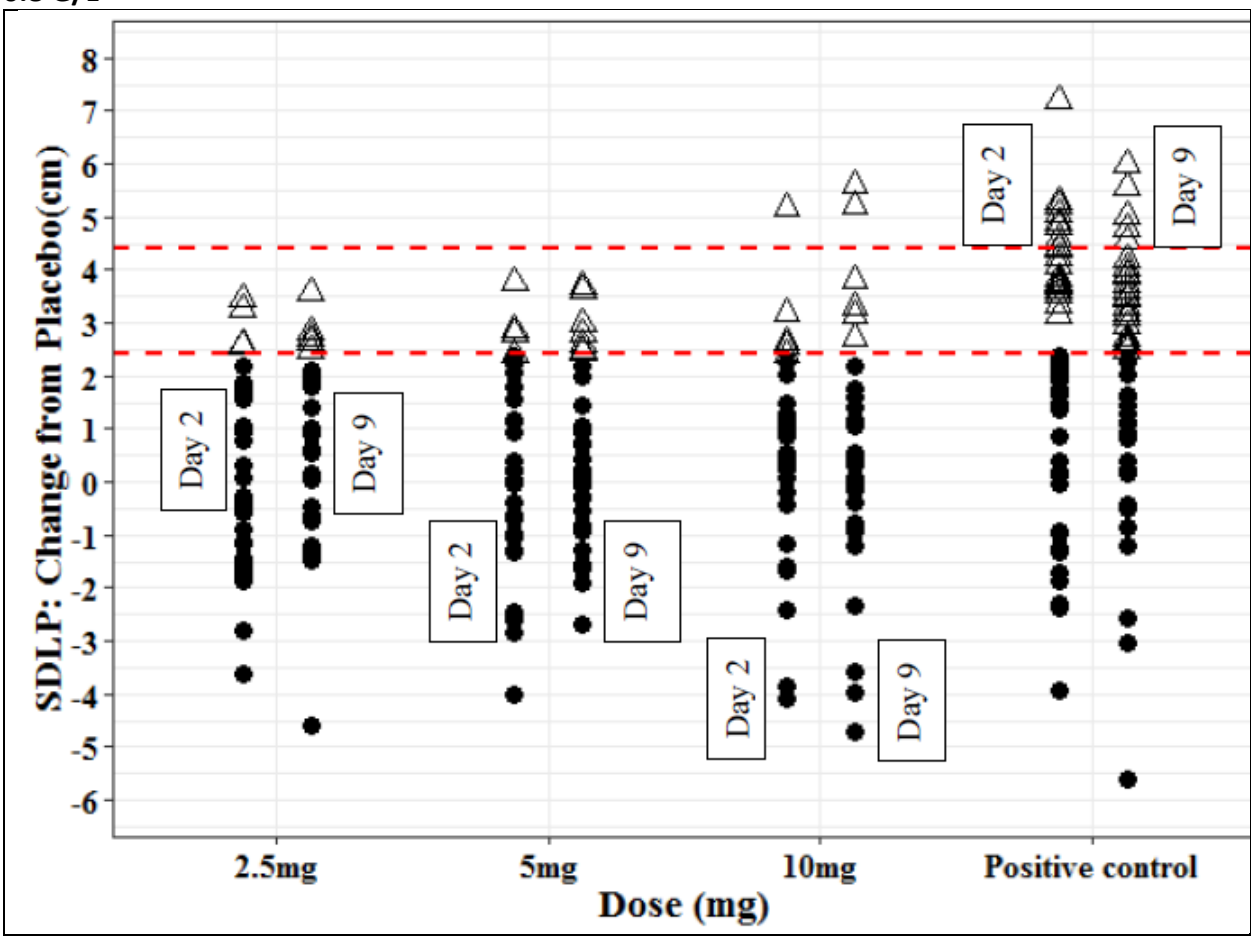
Table 106: Symmetry Analysis Results for SDLP

			Lemborexant		
	Day	Zopiclone 7.5 mg N=48	2.5 mg N=32	5 mg N=32	10 mg N=32
Subjects with a change from placebo in SDLP>2.4 cm	2	20	4	4	6
	9	25	6	7	6
Subjects with a change from placebo in SDLP<-2.4 cm	2	0	2	5	3
	9	3	1	1	3
Symmetry analysis p-value	2	<0.0001	0.698	1.000	0.508
	9	<0.0001	0.125	0.070	0.508

Abbreviations: p-value, probability value; SDLP, standard deviation of the lateral position
Source: FDA statistical reviewer's results (adpd.xpt)

Figure 62 shows the distribution of changes in SDLP on Day 2 and Day 9 across treatment groups. The data suggests that there are 2 out of 32 subjects had placebo-corrected SDLP>4.4 cm in 10 mg lemborexant group indicating that some subjects could have their ability to operate motor vehicle impaired. Blood alcohol legal limit of 0.8 g/L have been reported to be associated with average placebo-corrected SDLP changes of 4.4 cm. It should be noted that no subjects in lemborexant treatment group discontinued from the driving study.

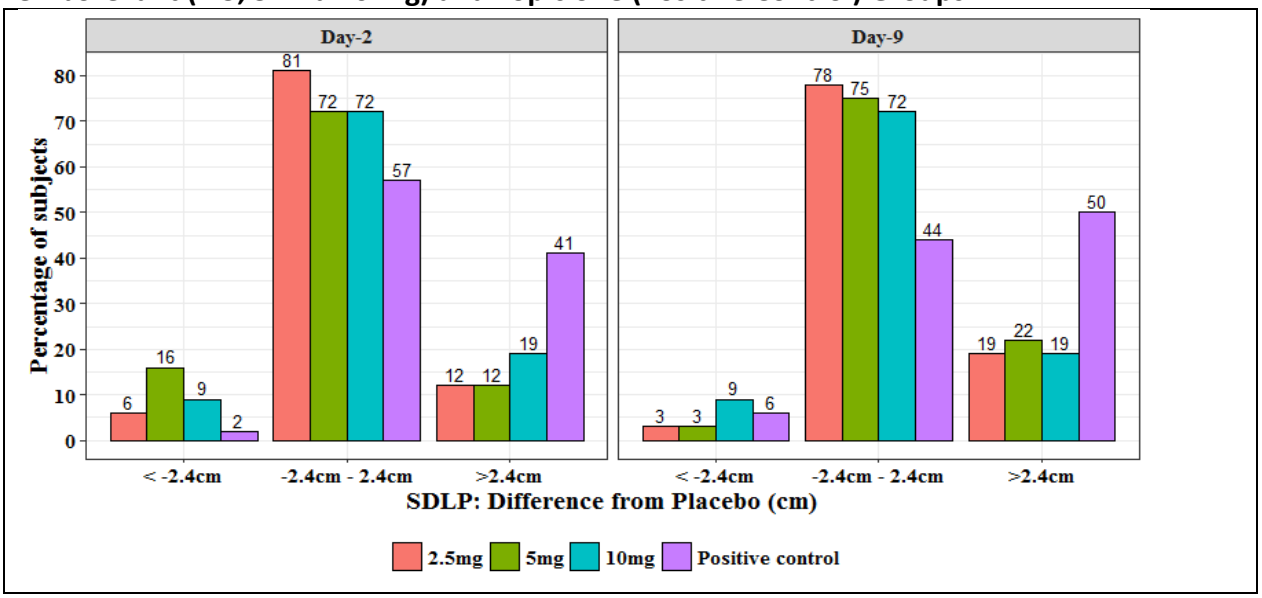
Figure 62: Placebo-Corrected Change in SDLP on Day 2 and Day 9 Across Treatment Groups. The Reference Lines at 2.4 and 4.4 cm Refer to SDLP Changes at Alcohol Limits of 0.5 G/L and 0.8 G/L



Abbreviation: SDLP, standard deviation of the lateral position
Source: FDA OCP Reviewer's analysis

No clear relationship between dose and proportion of patients with SDLP>2.4cm can be observed on Day 2 and Day 9.

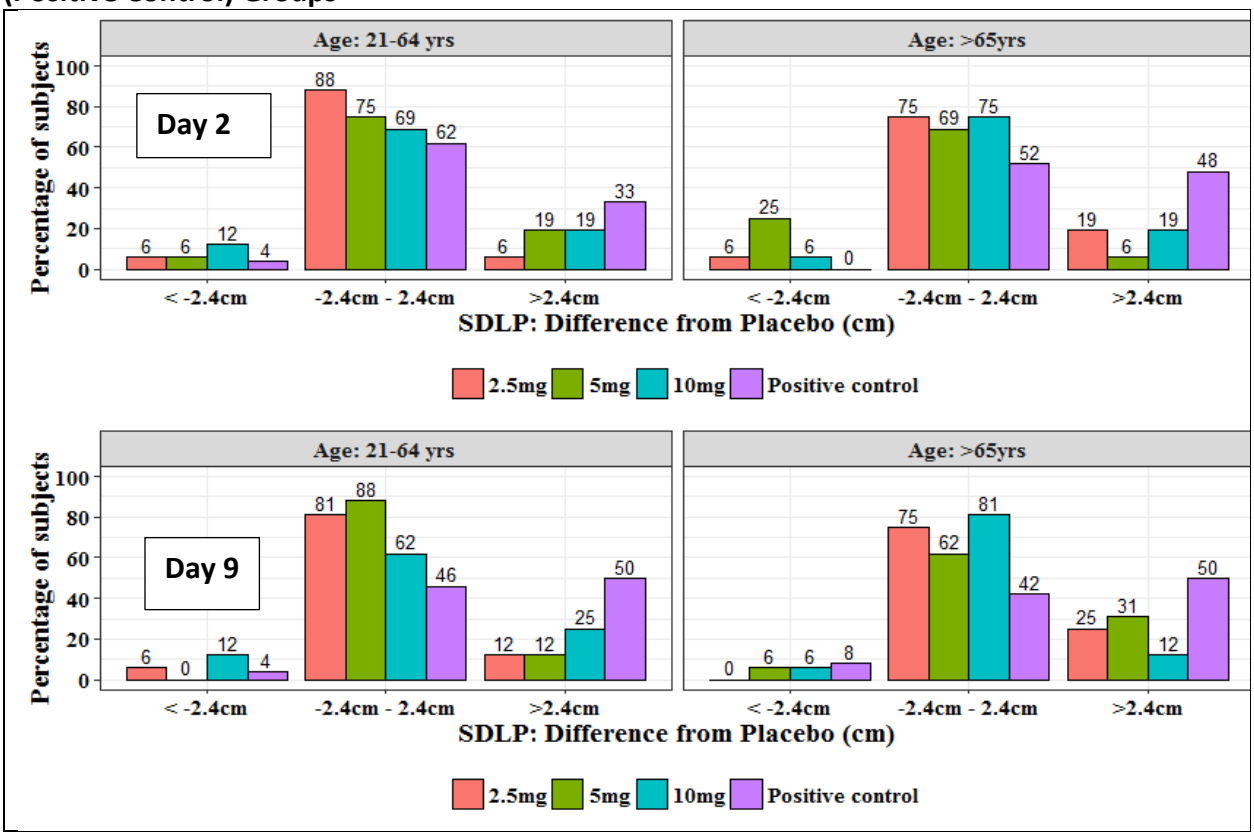
Figure 63: Proportion of Subjects With SDLP Changes (<-2.4 Cm, -2.4 To 2.4 Cm, >2.4cm) in Lemborexant (2.5, 5 And 10 Mg) and Zopiclone (Positive Control) Groups



Abbreviation: SDLP, standard deviation of the lateral position
Source: FDA OCP Reviewer's analysis

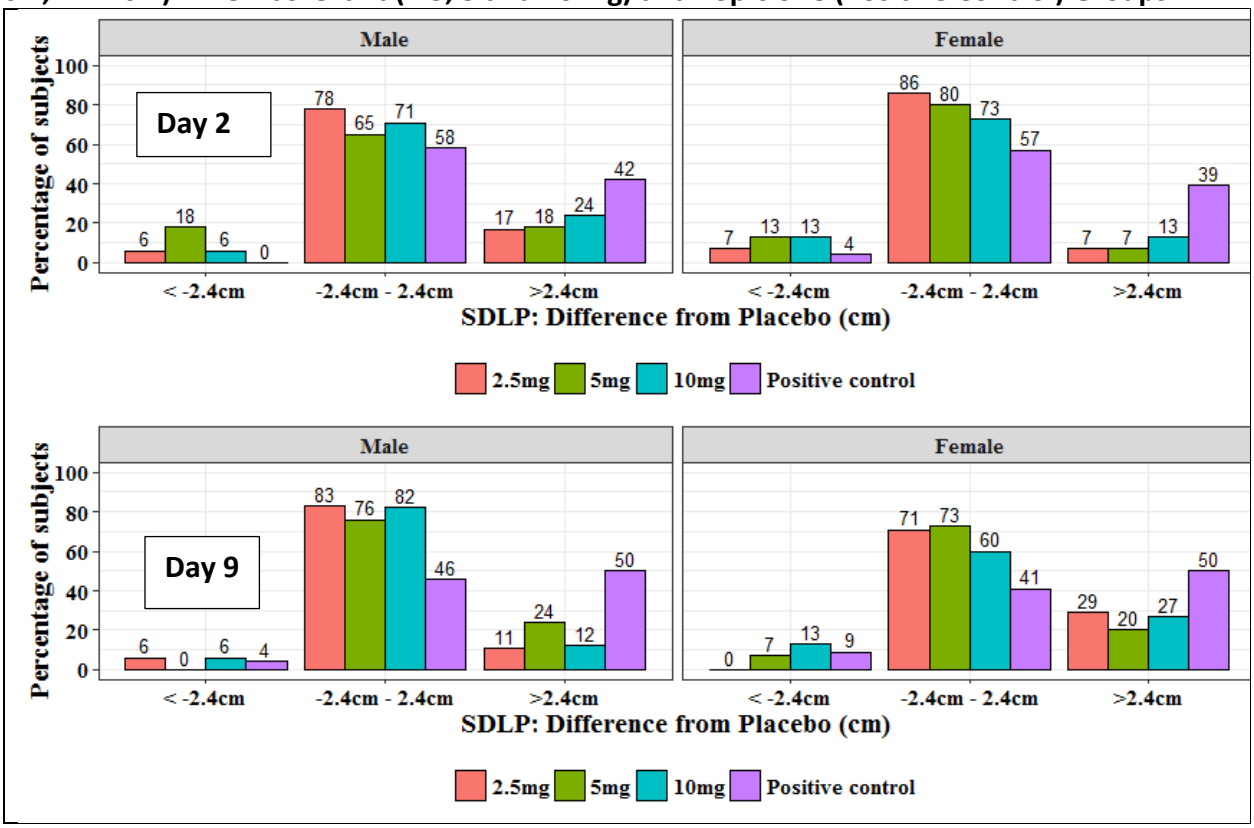
No relationship between dose and proportion of subjects with SDLP>2.4cm by age can be observed on Day 2 and Day 9 in Figure 13. Similarly, no relationship between dose and proportion of subjects with SDLP>2.4cm in male and female subjects can be observed on Day 2 and Day 9 in Figure 65.

Figure 64: Proportion of Non-Elderly (21-64 yrs) and Elderly (>65 yrs) Subjects with SDLP Changes (<-2.4 cm, -2.4 To 2.4 cm, >2.4 cm) in Lemborexant (2.5, 5 and 10 mg) and Zopiclone (Positive Control) Groups



Abbreviation: SDLP, standard deviation of the lateral position
Source: FDA OCP Reviewer's analysis

Figure 65: Proportion of Male and Female Subjects with SDLP Changes (<-2.4 cm, -2.4 to 2.4 cm, >2.4 cm) in Lemborexant (2.5, 5 and 10 mg) and Zopiclone (Positive Control) Groups

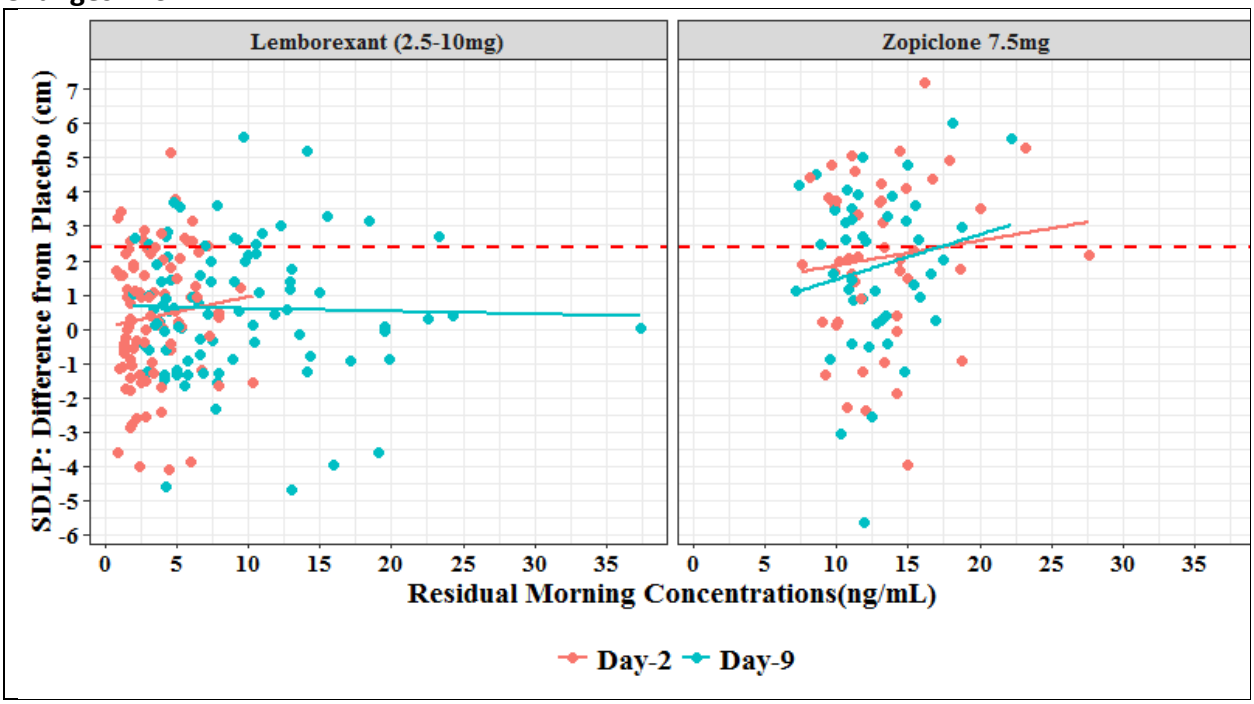


Abbreviation: SDLP, standard deviation of the lateral position
Source: FDA OCP Reviewer's analysis

Pharmacokinetic/Pharmacodynamic Analysis

Figure 66 shows the findings of linear regression analysis of the relationship between next-day residual concentrations of lemborexant and placebo-corrected SDLP changes. The 95% CI of the slope includes zero indicating a lack of statistically significant relationship. Figure 66 shows that some subjects have SDLP>2.4 cm or 4.4 cm across next-day residual lemborexant concentrations indicating the presence of inter-subject variability in the driving test.

Figure 66: Relationship Between Next-Day Residual Concentrations and Placebo-Corrected Changes in SDLP



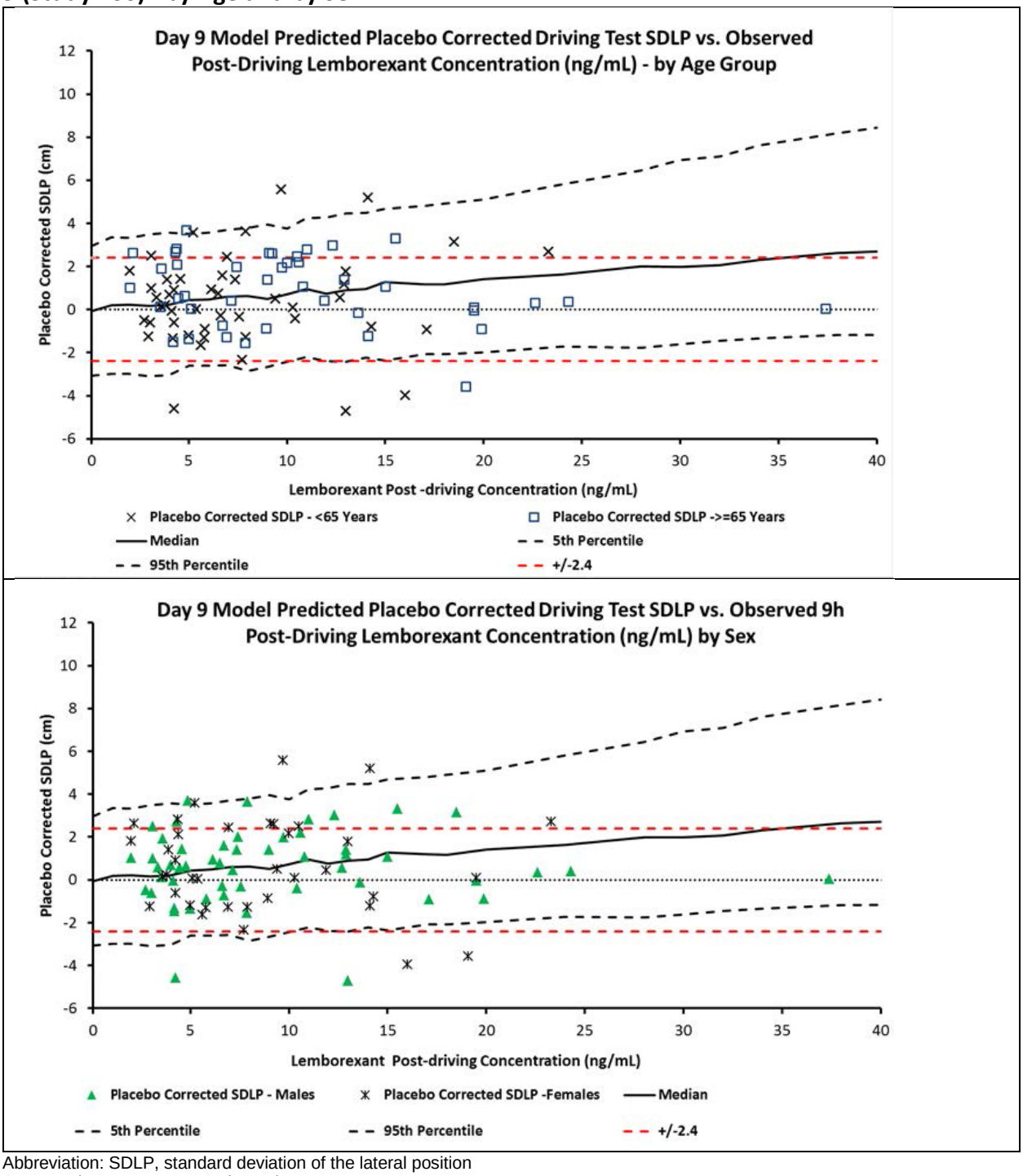
Abbreviation: SDLP, standard deviation of the lateral position
Note: Shown are data from lemborexant and zopiclone groups
Source: FDA OCP Reviewer's analysis

The Applicant also conducted PK/PD analysis and the findings are shown in Figure 67. Following multiple dosing of lemborexant 2.5, 5, and 10 mg for 8 days, a shallow statistically significant linear relationship was detected. This relationship appeared to be similar in adult and elderly, and in males and females, based on graphical evaluation of the large overlap of responses when split by age group and by sex.

Per applicant

Based on the large interindividual variability (60 to 70%) in response (SDLP) and noting that the predicted increases in SDLP at the highest lemborexant concentrations are below the clinically meaning threshold of 2.4 cm, the effect of observed lemborexant concentrations on SDLP is considered not clinically relevant.

Figure 67: Visual Predictive Check of Observed and Predicted Placebo-Corrected SDLP on Day 9 (Study 106) - by Age and by Sex



Abbreviation: SDLP, standard deviation of the lateral position
Source: Figure 5 on page 24 in study report

Discontinuation of driving study

No subjects were discontinued from the study. No drives were stopped for subjects on lemborexant. Three drives from 2 subjects were stopped prematurely after taking zopiclone.

Statistics Reviewer Comments: *The primary analysis results showed that the mean change of SDLP in lemborexant doses are less than 2.4 cm compared to placebo, suggesting their similarities to placebo. The symmetry test is not a proper test for the purpose of the study because statistical significance on the symmetry test is used to assess the strength of evidence* ***against*** *symmetry, not* ***for*** *symmetry. Lack of statistical significance does not necessarily suggest that the symmetry is demonstrated.*

OCP Reviewer Comments: *While the primary analysis suggests that the SDLP change in 2.5, 5 and 10 mg dose groups is not different from placebo, the label should mention that there is a potential for next-day residual effects in some patients taking 10 mg lemborexant. This recommendation is based on the observation that some subjects (6.3% (2 out of 32)) show placebo-corrected SDLP changes above 4.4 cm in lemborexant 10 mg dose group, which corresponds to a blood alcohol content of 0.8 g/L. No trends in placebo-corrected SDLP changes with higher concentrations of lemborexant are observed based on sex or age. Hence, no specific labeling language regarding the effects on placebo-corrected SDLP changes on the basis of age or sex are being proposed.*

14.4.4. Summary of Bioanalytical Method Validation and Performance

14.4.4.1. How Are the Active Moieties Identified and Measured in the Clinical Pharmacology and Biopharmaceutics Studies?

Lemborexant and its metabolites, M4, M9 and M10 concentrations in human plasma were measured by validated LC-MS/MS methods. The bioanalytical methods are considered to be adequately validated and acceptable.

Measurement of Lemborexant in Plasma

The similar bioanalytical methods for quantification of lemborexant and its metabolites in human plasma were developed and validated at (b) (4) (b) (4) independently. The method developed and validated by (b) (4) was used to support sample analysis in clinical Studies 001, 002, 003, 009, 012 104, 105, 106, 107 and 108. The method developed by (b) (4) were used to support sample analysis in Studies 004, 007, 008, 201, 202, 303, 304. The summary of bioanalytical methods and validation metrics is shown below. Both methods consist of a liquid-liquid extraction sample preparation after addition of stable isotope labelled internal standards (lemborexant-d3, M4-d3, M9-d3, and M10-d3). The resulting extracts were evaporated to dryness, reconstituted and then injected on a LC-MS column using a gradient method. Detection was done by tandem mass spectrometry in positive ESI mode with Triple Quad mass spectrometer.

Table 107: Summary Review of Bioanalytical Method Measuring Plasma Lemborexant and its Metabolites by (b) (4)

Bioanalytical Method Review Summary	**Method was adequately validated to support clinical studies**				
	Study Report RPT14206				
Company (b) (4)					
Analyte	Lemborexant			M4	
Material for calibration curve & concentration	Human Sodium Heparin Plasma			Human Sodium Heparin Plasma	
Internal Standard	Lemborexant-d3			M4-d3	
Validated Assay Range	0.0500 ng/mL to 50.0 ng/mL			0.0500 ng/mL to 50.0 ng/mL	
Recovery	Lemborexant: 76.7% to 78.7% Lemborexant-d3: 80.3% to 81.3%			M4: 76.7% to 80.9% M4-d3: 81.3% to 83.1%	
Carry over	No significant carry over observed			No significant carry over observed	
Regression Model & Weighting	Linear, weighted ($1/x^2$)				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		Lemborexant	Acceptability	M4	Acceptability
	Linearity	$R^2 \geq 0.9961$	Yes	$R^2 \geq 0.9973$	
QC concentrations	0.0500 (LLOQ), 150 (Low), 1.50 (Mid) and 40.0 (High) ng/mL			0.0500 (LLOQ), 150 (Low), 1.50 (Mid) and 40.0 (High) ng/mL	
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-7.0% to 12.0%	Yes	-7.8% to 10.7%	Yes
	Intra-run precision (%CV)	≤ 8.6%	Yes	≤ 14.7%	Yes
	Inter-run accuracy (%CV)	-2.0% to 6.0%	Yes	-3.6% to 5.3%	Yes
	Inter-run Precision (%CV)	≤ 6.4%	Yes	≤ 9.5%	Yes

Bioanalytical Method Review Summary	**Method was adequately validated to support clinical studies**				
Plasma sample bench-top stability	At least 21 hours			At least 21 hours	
Freeze/thaw stability	At least 3 cycles at ~-20°C and ~-70°C			At least 3 cycles at ~-20°C and ~-70°C	
Extract Sample Stability	At least 72 hours at ~4°C			At least 72 hours at ~4°C	
Autosampler stability	At least 172 hours at ~4°C			At least 172 hours at ~4°C	
Long-term frozen sample storage stability	At least 55 days at ~-20°C and at least 86 days at ~-70°C			At least 55 days at ~-20°C and at least 86 days at ~-70°C	
Stock Solution stability	At least 6 hours at room temperature and at least 62 days at ~-20°C			At least 6 hours at room temperature and at least 62 days at ~-20°C	
Analyte	M9			M10	
Material for calibration curve & concentration	Human Sodium Heparin Plasma			Human Sodium Heparin Plasma	
Internal Standard	M9-d3			M10-d3	
Validated Assay Range	0.0500 ng/mL to 50.0 ng/mL			0.0500 ng/mL to 50.0 ng/mL	
Recovery	M9: 78.1% to 78.3% M9-d3: 82.6% to 84.6%			M10: 76.3% to 77.8% M10-d3: 80.8% to 81.7%	
Carry over	No significant carry over observed			No significant carry over observed	
Regression Model & Weighting	Linear, weighted ($1/x^2$)				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		M9	Acceptability	M10	Acceptability
	Linearity	$R^2 \geq 0.9964$	Yes	$R^2 \geq 0.9965$	Yes
QC concentrations	0.0500 (LLOQ), 150 (Low), 1.50 (Mid) and 40.0 (High) ng/mL			0.0500 (LLOQ), 150 (Low), 1.50 (Mid) and 40.0 (High) ng/mL	
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-5.4% to 12.0%	Yes	-5.3% to 10.0%	Yes
	Intra-run precision (%CV)	≤ 7.1%	Yes	≤ 6.8%	Yes
	Inter-run accuracy (%CV)	-2.0% to 5.3%	Yes	0.3% to 5.3%	Yes
	Inter-run Precision (%CV)	≤ 6.9%	Yes	≤ 5.4%	Yes

Bioanalytical Method Review Summary	**Method was adequately validated to support clinical studies**	
Plasma sample bench-top stability	At least 21 hours	At least 21 hours
Freeze/thaw stability	At least 3 cycles at ~-20°C and ~-70°C	At least 3 cycles at ~-20°C and ~-70°C
Extract Sample Stability	At least 72 hours at ~4°C	At least 72 hours at ~4°C
Autosampler stability	At least 172 hours at ~4°C	At least 172 hours at ~4°C
Long-term frozen sample storage stability	At least 55 days at ~-20°C and at least 86 days at ~-70°C	At least 55 days at ~-20°C and at least 86 days at ~-70°C
Stock Solution stability	At least 6 hours at room temperature and at least 62 days at ~-20°C	At least 6 hours at room temperature and at least 62 days at ~-20°C

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; (b) (4) QC, quantitative computed

Table 108: Summary Review of Bioanalytical Method Measuring Urine Lemborexant by (b) (4)

Bioanalytical Method Review Summary	**Method was adequately validated to support clinical studies**		
	Study Report RPT11282		
Company: (b) (4)			
Analyte	Lemborexant		
Material for calibration curve & concentration	Human Urine		
Internal Standard	Lemborexant-d3		
Validated Assay Range	0.1 ng/mL to 100 ng/mL		
Recovery	Lemborexant: 6.2% to 10.5% Lemborexant-d3: 3.8% to 7.1%		
Carry over	No significant carry over observed		
Regression Model & Weighting	Linear, weighted ($1/x^2$)		
Validation Parameter	Method Validation Summary (Validation Report)		
Standard Curve Performance during accuracy and precision		Lemborexant	Acceptability
	Linearity	$R^2 \geq 0.9924$	Yes
QC concentrations	0.1 (LLOQ), 0.3 (Low), 3 (Mid), 80 (High), and 100 ng/mL		
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	7.0% to 16.0% (LLOQ) -1.9% to 11.2% (QCs)	Yes
	Intra-run precision (%CV)	≤ 16.4% (LLOQ) ≤ 6.2% (QCs)	Yes
	Inter-run accuracy (%CV)	11.0% (LLOQ) 0.0% to 7.2% (QCs)	Yes
	Inter-run Precision (%CV)	11.7% (LLOQ) ≤ 6.3% (QCs)	Yes

Bioanalytical Method Review Summary	Method was adequately validated to support clinical studies
Plasma sample bench-top stability	At least 24 hours
Freeze/thaw stability	At least 3 cycles
Autosampler stability	At least 172 hours at ~4°C
Long-term frozen sample storage stability	At least 94 days at -20°C and -70°C
Stock Solution stability	At least 6 hours at room temperature and at least 95 days at ~-20°C

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; (b) (4); QC, quantitative computed

Table 109: Summary Review of Bioanalytical Method Measuring Plasma Lemborexant and Its Metabolites by (b) (4)

Bioanalytical Method Review Summary	Method was adequately validated to support clinical studies				
	Study Report AHTR2				
Company: (b) (4)					
Analyte	Lemborexant			M4	
Material for calibration curve & concentration	Human Plasma			Human Plasma	
Internal Standard	Lemborexant-d3			M4-d3	
Validated Assay Range	0.0500 to 50.0 ng/mL			0.0500 to 50.0 ng/mL	
Average Recovery	Lemborexant: 73.0% Lemborexant-d3: 71.7%			M4: 73.1% M4-d3: 70.7%	
Carry over	No significant carry over observed			No significant carry over observed	
Regression Model & Weighting	Linear, weighted ($1/x^2$)				
Validation Parameter	Method Validation Summary (Validation Report)				
Standard Curve Performance during accuracy and precision		Lemborexant	Acceptability	M4	Acceptability
	Linearity	$R^2 \geq 0.9900$	Yes	$R^2 \geq 0.9900$	Yes
QC concentrations	0.0500, 0.150, 0.400, 1.50, 6.00, and 37.5 ng/mL			0.0500, 0.150, 0.400, 1.50, 6.00, and 37.5 ng/mL	
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-0.0515% to 11.2%	Yes	0.834% to 10.6%	Yes
	Intra-run precision (%CV)	0.819% to 12.0%	Yes	0.595% to 13.1%	Yes
	Inter-run accuracy (%CV)	3.51% to 7.73%	Yes	2.31% to 8.32%	Yes
	Inter-run Precision (%CV)	2.06% to 7.37%	Yes	1.81% to 7.50%	Yes

Bioanalytical Method Review Summary	**Method was adequately validated to support clinical studies**			
Plasma sample bench-top stability	Two hours at room temperature and in an ice bath		Two hours at room temperature and in an ice bath	
Freeze/thaw stability	Five cycles thawed at room temperature and frozen at -20 °C and -70 °C		Five cycles thawed at room temperature and frozen at -20 °C and -70 °C	
Extract Sample Stability	225 hours at 2 to 8 °C		225 hours at 2 to 8 °C	
Stock Solution stability	518 days at -20 °C in acetonitrile; 13 days at -20 °C in acetonitrile: H_2O: formic acid (50:50:0.01)		13 days at -20 °C in acetonitrile; 13 days at -20 °C in acetonitrile: H2O: formic acid (50:50:0.01)	
Analyte	M9		M10	
Material for calibration curve & concentration	Human Plasma		Human Plasma	
Internal Standard	M9-d3		M10-d3	
Validated Assay Range	0.0500 to 50.0 ng/mL		0.0500 to 50.0 ng/mL	
Average Recovery	M9: 73.6% M9-d3: 70.9%		M10: 73.7% M10-d3: 71.4%	
Carry over	No significant carry over observed		No significant carry over observed	
Regression Model & Weighting	Linear, weighted ($1/x^2$)			
Validation Parameter	Method Validation Summary (Validation Report)			
Standard Curve Performance during accuracy and precision		M9	Acceptability	M10	Acceptability
	Linearity	$R^2 \geq 0.9900$	Yes	$R^2 \geq 0.9900$	Yes
QC concentrations	0.0500, 0.150, 0.400, 1.50, 6.00, and 37.5 ng/mL		0.0500, 0.150, 0.400, 1.50, 6.00, and 37.5 ng/mL	
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	-0.265% to 7.54%	Yes	0.676% to 6.98%	Yes
	Intra-run precision (%CV)	1.16% to 13.1%	Yes	0.253% to 11.2%	Yes
	Inter-run accuracy (%CV)	0.642% to 4.95%	Yes	1.34% to 8.15%	Yes
	Inter-run Precision (%CV)	1.61% to 7.61%	Yes	2.43% to 7.15%	Yes
Plasma sample bench-top stability	Two hours at room temperature and in an ice bath		Two hours at room temperature and in an ice bath	
Freeze/thaw stability	Five cycles thawed at room temperature and frozen at -20 °C and -70 °C		Five cycles thawed at room temperature and frozen at -20 °C and -70 °C	
Extract Sample Stability	225 hours at 2 to 8 °C		225 hours at 2 to 8 °C	
Stock Solution stability	13 days at -20 °C in acetonitrile; 13 days at -20 °C in acetonitrile : H_2O : formic acid (50:50:0.01)		13 days at -20 °C in acetonitrile; 13 days at -20 °C in acetonitrile: H_2O: formic acid (50:50:0.01)	

Abbreviations: CV, coefficient of variation; [redacted] (b) (4); QC, quantitative computed

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/s/

KEITH J KIEDROW
12/20/2019 03:23:50 PM

AMY M AVILA
12/20/2019 03:24:49 PM

AISAR H ATRAKCHI
12/20/2019 03:26:23 PM

PAUL C BROWN
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XIAOLEI N PAN
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VISHNU D SHARMA
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VENKATESH A BHATTARAM
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XINYUAN ZHANG on behalf of YUCHING N YANG
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XINYUAN ZHANG
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LUNING ZHUANG
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PEILING YANG
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HSIEN MING J HUNG
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MICHELLE S HORNER
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MICHAEL C DAVIS
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TIFFANY R FARCHIONE
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ELLIS F UNGER
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	212,028/0000
Drug Name:	Lemborexant
Indication:	Insomnia
Study number:	E2006-A001-103
Applicant:	Eisai Inc.
Date(s):	Date of Document: 12/27/2018 PDUFA date: 10/27/2018 Completion date: 5/29/2018
Review Priority:	S
Biometrics Division:	DB VI
Statistical Reviewer:	Ling Chen, Ph.D., Expert Mathematical Statistician, CSS supporting team/DBVI/OB
Concurring Reviewers:	Qianyu Dang, Ph.D., Lead Statistician, CSS supporting team/DBVI/OB
Medical Division:	Controlled Substance Staff
The CSS Team:	Katherine Bonson, Ph.D., Pharmacologist, OD/CSS Silvia Calderon, Ph.D., Senior Pharmacologist, OD/CSS Dominic Chiapperino, Ph.D., Acting Director, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS

Keywords: Crossover design; Human abuse potential study; Self-reported endpoint; Sedatives

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1. Executive Summary

The applicant, Eisai Inc., submitted the results from the human abuse potential study E2006-a001-103 for the assessment of abuse potential of lemborexant.

Study E2006-a001-103 was a single-dose, randomized, double-blind, placebo- and active-controlled crossover study. The primary objective was to evaluate the abuse potential of single oral doses of lemborexant (10 mg, 20 mg and 30 mg) compared to placebo in healthy, non-dependent recreational sedative users. One of the secondary objectives was to assess the abuse potential of single oral doses of lemborexant relative to 30 mg zolpidem and 40 mg suvorexant in the same study population.

Thirty-nine subjects were randomized to the Treatment Phase, and 32 (82.1%) subjects completed the study.

The reviewer's analyses were on the primary endpoint Drug Liking Emax, and the key secondary endpoints Good Effects Emax, High Emax, Overall Drug Liking Emax and Take Drug Again Emax. The descriptive statistics for secondary endpoints Stoned Emax, Bad Effects Emax, Alertness/Drowsiness Emin and Any Effects Emax were also included in this report.

The issue in this study was that the study failed the validation test with the prespecified test value 15. Based on the FDA 2017 Guidance, it was a failed study. In this reviewer's opinion, the reasons of failing the validation test were 1) three and 6 subjects did not respond to 30 mg zolpidem and 40 mg suvorexant (Drug Liking Emax score <55), respectively; and 2) four subjects responded to placebo with a large Drug Liking Emax score (≥89, see page 13 of this report). The sponsor's arguments and the reviewer's discussion on this issue can be found on pages 18 and 19.

The reviewer performed analysis based on 32 completers by assuming that the sponsor proposed test value 11 for the validation test in the Amendment 2 after unblinding the study was acceptable. The reviewer's primary analysis showed that for Drug Liking Emax,

- LSMeans produced by both 40 mg suvorexant and 30 mg zolpidem were significantly larger than that produced by placebo by 11 points (p=0.0251 and 0.0065, respectively);
- LSMean produced by 30 mg lemborexant (83.9) was significantly larger than that produced by 40 mg suvorexant (76.5, p=0.0233), and LSMean produced by 40 mg suvorexant was not significantly larger than those produced by 10 mg and 20 mg lemborexant (78.9 and 80.9, $p \geq 0.7372$);
- LSMean produced by 30 mg zolpidem (78.5) was not significantly larger than those produced by 3 lemborexant doses ($p \geq 0.5376$).

The reviewer's secondary analysis showed that

- LSMeans produced by 3 lemborexant doses for Good Effects Emax (65.3, 72.3, and 78.1) were significantly larger than that produced by 40 mg suvorexant (51.5, $p \leq 0.0178$), and LSMeans produced by 3 lemborexant doses for High Emax (60.6, 65.4, and 82.2) were also significantly larger than that produced by 40 mg suvorexant (39.7, $p \leq 0.0009$);

- LSMean produced by for 30 mg zolpidem was not significantly larger than those produced by 3 lemborexant doses for Good Effects Emax and High Emax ($p \geq 0.2345$), with an exception that LSMean produced by 30 mg lemborexant (82.2) was significantly larger than that produced by 30 mg zolpidem for High Emax (65.4, p=0.0061);
- none of the mean or median differences between each positive control and each dose of lemborexant was significantly greater than zero for Overall Drug Liking Emax and Take Drug Again Emax ($p \geq 0.3057$).

The descriptive statistics showed that all doses of lemborexant had larger means in Stoned Emax and Bad Effects Emax compared to 40 mg suvorexant, and larger means in Any Effects Emax compared to both 40 mg suvorexant and 30 mg zolpidem. The means of Alertness/Drowsiness Emin produced by 3 lemborexant doses were smaller than those produced by 40 mg suvorexant and 30 mg zolpidem.

The reviewer also performed the sensitivity analysis by eliminating 3 subjects who had negative difference in maximum liking between both positive controls and placebo. Based on the data from 29 subjects, both positive controls passed the validation test with the prespecified test value 15 ($p \leq 0.0128$). The test results from the comparisons between positive controls and each dose of lemborexant based on 32 subjects and 29 subjects were the same for the primary and key secondary endpoints with an exception that for Drug Liking Emax LSMean produced by 30 mg lemborexant was significantly larger than that produced by 40 mg suvorexant in the primary analysis but the difference was not significant in the sensitivity analysis.

In conclusion, the abuse potential of lemborexant may be similar to zolpidem but larger than suvorexant.

2. Review report on Study E2006-a001-103

2.1. Overview

Study E2006-a001-103 was a randomized, double-blind, 6-way crossover study to determine the abuse potential of single oral doses of lemborexant compared to zolpidem, suvorexant and placebo in healthy, non-dependent, recreational sedative users.

2.1.1. Objectives of the study

Primary Objective:

- To evaluate the abuse potential of single oral doses of lemborexant compared to placebo in healthy, non-dependent recreational sedative users as determined by the peak maximum effect (Emax) for Drug Liking ("at this moment") visual analog scale (VAS).

Secondary Objectives:

- To confirm the abuse potential of single oral doses of zolpidem and suvorexant compared to placebo in healthy, non-dependent, recreational sedative users as determined by the Emax for Drug Liking ("at this moment") VAS, in order to confirm study validity;
- To assess the abuse potential of single oral doses of lemborexant relative to zolpidem and suvorexant in healthy, non-dependent, recreational sedative users as determined by the Emax for Drug Liking ("at this moment") VAS;
- To evaluate the safety and tolerability of single oral doses of lemborexant compared to zolpidem, *suvorexant, and placebo, in healthy, non-dependent, recreational sedative users.*

Reviewer's Comments: Even though the primary objective was to evaluate the abuse potential of lemborexant compared to placebo, according to the gatekeeping testing procedure recommended in the FDA 2017 Guidance, the relative abuse potential of lemborexant compared to zolpidem and suvorexant were assessed before the assessment of the abuse potential of lemborexant compared to placebo in this review report. If the study did not demonstrate significantly lower abuse potential for lemborexant compared to either zolpidem or suvorexant, the comparison between lemborexant and placebo was not performed.

2.1.2. Study design

This study consisted of 3 phases: Qualification, Treatment, and Follow-up.

The Qualification Phase consisted of a Screening Period (Visit 1) and a Qualification Period (Visit 2). Subjects who met the inclusion and exclusion criteria during Screening continued to the Qualification Period, which occurred within 30 days of the Screening Period. During the Qualification Period, subjects were confined to the clinical site from Day −1 until Day 10. Each subject received a single treatment of zolpidem (30 mg), suvorexant (40 mg), and placebo in a randomized, double-blind, 3-period crossover, double-dummy fashion, with each dose separated by a washout period of approximately 3 days. Pharmacodynamic (PD) and safety assessments were performed.

Subjects who met eligibility criteria during the Qualification Period and met the inclusion and exclusion criteria continued to the Treatment Phase of the study after at least a 7-day washout between the last study drug administered during the Qualification Period and the first study drug administered during the Treatment Phase. The Treatment Phase consisted of 6 treatment periods (Visits 3 to 8) with washout periods of at least 14 days between treatments. During each Treatment Period, subjects were confined to the clinical site from Day −1 until Day 4. Throughout the Treatment Phase, each subject received a single treatment of lemborexant (10 mg, 20 mg, and 30 mg), zolpidem (30 mg), suvorexant (40 mg), and placebo in a randomized, double-blind, triple-dummy fashion. In each Treatment Period, PD, pharmacokinetic (PK), and safety assessments were performed.

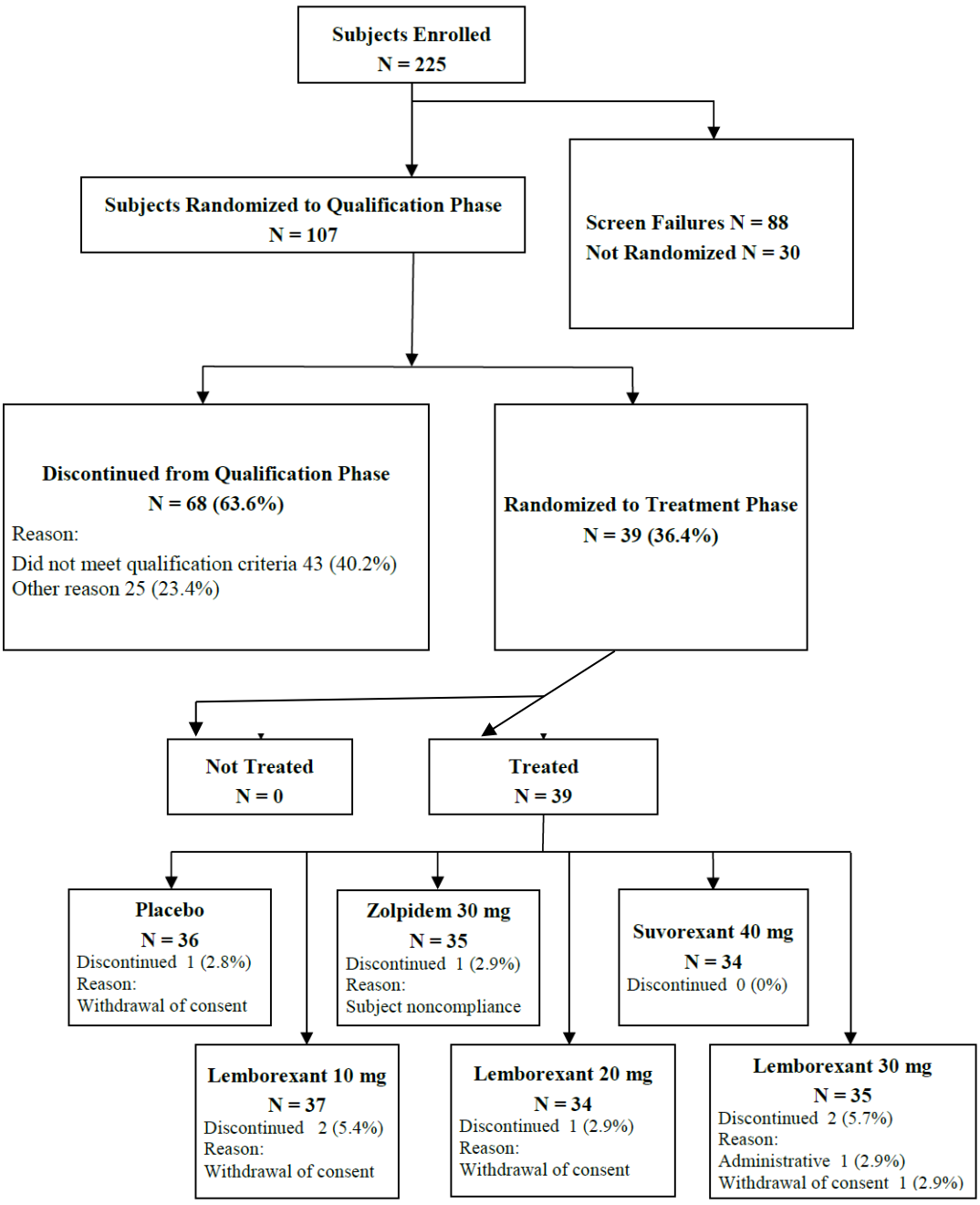
The Follow-up Phase consisted of a Follow-up Visit (Visit 9) and occurred approximately 14 days after the last study drug administration or at the time of early discontinuation.

2.1.3. Qualification Phase Eligibility Criteria

1. Ability to distinguish orally administered 30 mg zolpidem and 40 mg suvorexant from placebo on the bipolar Drug Liking ("at this moment") VAS, defined as ≥15-point peak increase for Drug Liking in response to zolpidem and suvorexant relative to placebo following drug administration. A peak score of ≥65 must have been indicated on the bipolar measure of Drug Liking ("at this moment") in response to zolpidem and suvorexant.
2. Displayed an acceptable placebo response, defined as a VAS response between 40 to 60 inclusive, for peak (Emax) Drug Liking ("at this moment").
3. Demonstrated responses to zolpidem and suvorexant that are consistent with discrimination relative to placebo on other subjective measures, as judged by the study center staff.
4. Tolerated study treatment (e.g., no episodes of vomiting within the first 3 hours post dose) and demonstrated ability to complete the PD assessments (e.g., no unarousable sedation within 4 hours post dose).
5. Demonstrated general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

2.1.4. Study Subjects

The following flow chart combines Figures 2 and 3 in the study report, and shows subject disposition and reason for discontinuation in the Qualification Phase and Treatment Phase.



2.1.5. Abuse potential endpoints

Primary endpoint

Emax for Drug Liking ("at this moment") VAS

Secondary Endpoints

- Balance of effects
  - Drug Liking VAS (time to peak effect [TEmax], peak minimum effect [Emin], time to peak minimum effect [TEmin], and time-averaged area under the effect curve

[TA_AUE])

- Global
  - Overall Drug Liking VAS (Emax)
  - Take Drug Again VAS (Emax)
  - SDV (Emax)
- Positive effects
  - Good Effects VAS (Emax, TEmax, TA_AUE)
  - Stoned VAS (Emax, TEmax, TA_AUE)
  - High VAS (Emax, TEmax, TA_AUE)
- Global
  - Overall Drug Liking VAS (Emax)
  - Take Drug Again VAS (Emax)
  - SDV (Emax)
- Positive effects
  - Good Effects VAS (Emax, TEmax, TA_AUE)
  - Stoned VAS (Emax, TEmax, TA_AUE)
  - High VAS (Emax, TEmax, TA_AUE)
- Negative effects
  - Bad Effects VAS (Emax, TEmax, TA_AUE)
- Sedative effects
  - Alertness/Drowsiness VAS (Emax, TEmax, TA_AUE) (see Section 9.8.3.2 for changes)
  - ARCI PCAG scale (Emax, TEmax, and TA_AUE)
- Other drug effects
  - Any Effects (Emax, TEmax, and TA_AUE)
- Objective and observer-rated measures of sedation and cognitive impairment
  - OAA/S (E_{max} and TA_AUE of composite and sum scores) (see Section 9.8.3.2 for Changes in the study report)
  - CRT (maximum change from baseline [CFB_{max}] and TA_AUE of MRT, RRT, and TRT; minimum change from baseline [CFB_{min}] and TA_AUE of percentage correct)
  - DAT (CFB_{max} and TA_AUE of MRT, RRT, and TRT; CFB_{min} and TA_AUE of
    - percentage correct) (see Section 9.8.2 and 9.8.3.1 for changes in the study report)

2.1.6. Statistical methodologies used in the Sponsor's analyses

The Completers Analysis Set was used for all analysis on the primary endpoint, Drug Liking Emax. All other PD analyses were performed on the PD Analysis Set. The PD endpoints for the Treatment Phase were analyzed using a mixed-effect model if the distribution of the residuals was normal. The model included treatment, period, treatment sequence, and first-order carryover effect (where applicable) as fixed effects, baseline (predose) measurements as covariate (where applicable), and subject nested within treatment sequence as a random effect. If the carryover effect was found to be nonsignificant at the alpha=0.25 level of significance, then the term was dropped from the analysis model. The residuals from each mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed under the assumption of a normal distribution if the P value of the test was ≥ 0.05. If the normality assumption of the model was satisfied, least-squares means (LSMs), SE, and 95% confidence

intervals (CIs) for treatments and treatment differences were derived from the mixed-effects model. *P* values were provided for the effects and the contrasts. If the normality assumption of the model was not satisfied, the Wilcoxon sign-rank test was used. Median, Q1–Q3, and the *P* value of the paired difference were presented.

Reviewer's comments: The planned analysis did not include checking the model assumption of homogeneity variances. In addition, the Wilcoxon signed-rank test has an assumption that the distribution of paired differences should be symmetric. The reviewer checked the review report on the SAP written by the reviewer Dr. Anna Sun. The following was one of her comments on the SAP:
If the data appears relatively unskewed and is moderately symmetric, then a paired t-test may be performed for the PD parameter. If the data appears highly skewed, then the Wilcoxon sign-rank test may be used to compare median differences.
The highlighted recommendation was wrong. The sponsor changed Wilcoxon Signed Rank test to the Sign test in their Amendment 2 on the SAP after unblinding the study, and reported the results from the Sign test instead of the Wilcoxon Signed Rank test in the study report.

According to FDA 2017 Guidance for the primary endpoint, Drug Liking Emax, the following hypotheses were tested:

1. H_a: $\mu_C - \mu_P \leq 15$ vs. H_a: $\mu_C - \mu_P > 15$ *(Study validation);*
2. H_0: $\mu_C \leq \mu_P$ vs. H_a: $\mu_C > \mu_P$ *(Assess relative abuse potential);*
3. H_0: $\mu_T - \mu_P \geq 11$ vs. H_a: $\mu_T - \mu_P < 11$ *(Assess abuse potential compared to placebo).*

Reviewer's comments: The sponsor changed margin for the validation test from 15 to 11, after treatment unblinding (See Section 9.8.3.1. in the study report). Please see the sponsor's arguments for this change, and the reviewer's discussion on pages 17 and 18 of this review report.

For all key secondary endpoints, the hypotheses for the comparisons between each positive control and placebo as well as between each dose of lemborexant and each positive control were prespecified as the same as those in the primary analysis. For non-key secondary endpoints, 2- sided tests with a test value zero were used. A p-value less than 0.05 was considered statistically significant for all individual 1-sided and 2-sided hypothesis tests.

2.1.7. Summary of Sponsor Reported Analysis Results

- Drug Liking VAS mean Emax was statistically significantly higher for zolpidem and suvorexant compared to placebo, confirming study validity with a validation margin of 11. The 20.5-point and 18.3-point higher mean Drug Liking VAS Emax scores for zolpidem and suvorexant, respectively, compared to placebo did not reach statistical significance using a validation margin of 15.

- Mean Emax values for the primary study endpoint, Drug Liking VAS, were not associated with statistically significantly different scores for lemborexant (10 mg, 20 mg, and 30 mg) compared to both zolpidem (30 mg) and suvorexant (40 mg).
- Global drug effects, as reflected by the Overall Drug Liking VAS and Take Drug Again VAS Emax scores, for all doses of lemborexant were not statistically significantly different compared to the active comparators, indicating that the subjective overall liking and willingness to take the drug again were similar to that of the active comparators.
- Mean SDV Emax values were similar for all doses of lemborexant and the active comparators (i.e., ranging from $13.74 to $16.92), with subjects most valuing lemborexant 20 mg and zolpidem. The mean peak subjective drug value assigned to placebo was low ($2.65).
- Positive subjective effects were assessed using the Good Effects VAS, High VAS, and Stoned VAS. Mean Emax scores for all doses of lemborexant were not statistically significantly different compared to the active comparators on the Good Effects VAS or High VAS. None of the doses of lemborexant were associated with statistically significant differences from zolpidem on the Stoned VAS Emax but statistically significantly higher scores were observed as compared to suvorexant.
- Negative subjective effects were assessed using the Bad Effects VAS. The active drugs, including all 3 doses of lemborexant, were associated with statistically significantly elevated Bad Effects VAS Emax scores compared to placebo. At the lowest dose, lemborexant (10 mg) had a statistically significantly lower Emax score compared to zolpidem. All doses of lemborexant were associated with statistically significantly higher mean Emax scores on the Bad Effects VAS compared to suvorexant.
- Negative subjective effects were assessed using the Bad Effects VAS. The active drugs, including all 3 doses of lemborexant, were associated with statistically significantly elevated Bad Effects VAS Emax scores compared to placebo. At the lowest dose, lemborexant (10 mg) had a statistically significantly lower Emax score compared to zolpidem. All doses of lemborexant were associated with statistically significantly higher mean Emax scores on the Bad Effects VAS compared to suvorexant.
- Other drug effects were assessed using the Any Effects VAS. At the highest dose, lemborexant (30 mg) was associated with statistically significantly higher mean Emax compared to zolpidem. All doses of lemborexant were associated with statistically significantly higher mean Emax scores on the Any Effects VAS compared to suvorexant.
- Subjective feelings of drowsiness were assessed using the Alertness/Drowsiness VAS. Compared to both zolpidem and suvorexant, all doses of lemborexant were associated with statistically significantly lower mean Emin scores, indicating increased drowsiness.
- Sedative subjective effects were assessed using the PCAG subscale of the ARCI questionnaire, while objective effects of sedation were assessed using the OAA/S. The 2 highest doses of lemborexant (20 mg and 30 mg) were associated with statistically significantly increased sedation compared to suvorexant, but not zolpidem, on the PCAG. Observed effects of sedation as measured by the composite score of the OAA/S revealed that the 2 highest doses of lemborexant were associated with statistically significantly increased sedation compared to suvorexant, and results for the sum score of the OAA/S showed that highest dose of lemborexant was associated with statistically significantly increased sedation compared to suvorexant.

2.2. Data Location

The datasets used in the reviewer's analysis are located at
\\cdsesub1\evsprod\NDA212028\0000\m5\datasets\e2006-a001-103\analysis\adam\datasets

2.3. Reviewer's Assessment

In this report, the reviewer used the following notations for treatments in Study E2006-a001-103.
L10 – 10 mg lemborexant
L20 – 20 mg lemborexant
L30 – 30 mg lemborexant
P – Placebo
S40 – 40 mg suvorexant
Z30 – 30 mg zolpidem

2.3.1. Primary Analysis

2.3.1.1. Descriptive statistics

Figure 1 is the heat map display for each subject's maximum liking score by treatment.

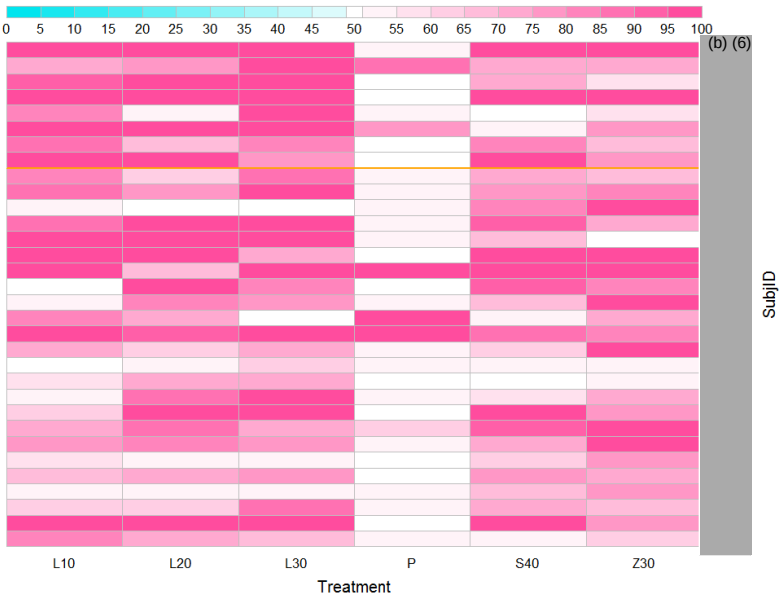


Figure 1: Heat Map by Treatment for Drug Liking Emax

The orange line on the heat map separates females from males. Note that 6 subjects (b) (6) had a maximum score less than 55 for 40 mg suvorexant. Three subjects, (b) (6) did not respond to 30 mg zolpidem (Emax scores less than 55). Three subjects (b) (6) had a maximum liking score of 100, and one subject (b) (6) had a maximum liking score of 89 for placebo. Subjects (b) (6) had larger maximum liking for placebo (89, 79 and 100, respectively). For these three subjects, the difference between 40 mg suvorexant and placebo were -16, -49 and -28, and the difference between 30 mg zolpidem and placebo were -17, -27 and -2. These

negative numbers greatly affected the mean difference between these two treatments as well as inter subject variability.

Table 1 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for the primary endpoint Drug Liking Emax.

Table 1: Summary statistics for Drug Liking Emax (N=32)

TRT	Mean	SD	Min	Q1	Med	Q3	Max
L10	78.4	18.5	50	59.75	83	98.75	100
L20	80.5	17.7	50	66.25	80.5	99.75	100
L30	83.6	17.1	50	73.5	84.5	100	100
P	57.8	16.2	50	50	51	51	100
S40	76.1	17.8	50	62	73	93.75	100
Z30	78.3	16.0	50	67.75	76.5	97	100

As summarized in Table 1, lemborexant (10 mg, 20 mg and 30 mg) had the mean of maximum liking scores greater than both 40 mg suvorexant and 30 mg zolpidem. The mean of placebo responses was 57.8 with a standard deviation 16.2.

Table 2 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for differences between treatments for Drug Liking Emax.

Table 2: Summary statistics for the differences between treatments for Drug Liking Emax (N=32)

TRT Diff	Mean	SD	Min	Q1	Med	Q3	Max
S40-P	18.3	24.4	-49	0.5	20	39.5	50
Z30-P	20.5	21.2	-27	2.25	23	34.5	50
S40-L10	-2.3	20.3	-49	-10.75	0	6.75	44
S40-L20	-4.4	17.2	-47	-15	-0.5	6	33
S40-L30	-7.5	20.4	-50	-21.25	-7	1	33
Z30-L10	-0.1	23.3	-50	-19	-1	20.5	49
Z30-L20	-2.2	21.8	-50	-19.75	-2	9.75	50
Z30-L30	-5.3	24.2	-50	-22.75	-7.5	21.25	50
L10-P	20.6	20.8	-17	0.25	18.5	38.5	50
L20-P	22.7	23.7	-30	2	24	49	50
L30-P	25.8	22.4	-50	11.25	26.5	48.75	50

The mean and median differences between 40 mg suvorexant and all doses of lemborexant, and between 30 mg zolpidem and all doses of lemborexant were smaller than or equal to zero. The mean and median

differences between each dose of lemborexant and placebo were greater than or equal to 20.6 and 18.5, respectively. Figure 2 is the boxplots for each treatment as well as treatment differences for Drug Liking Emax.

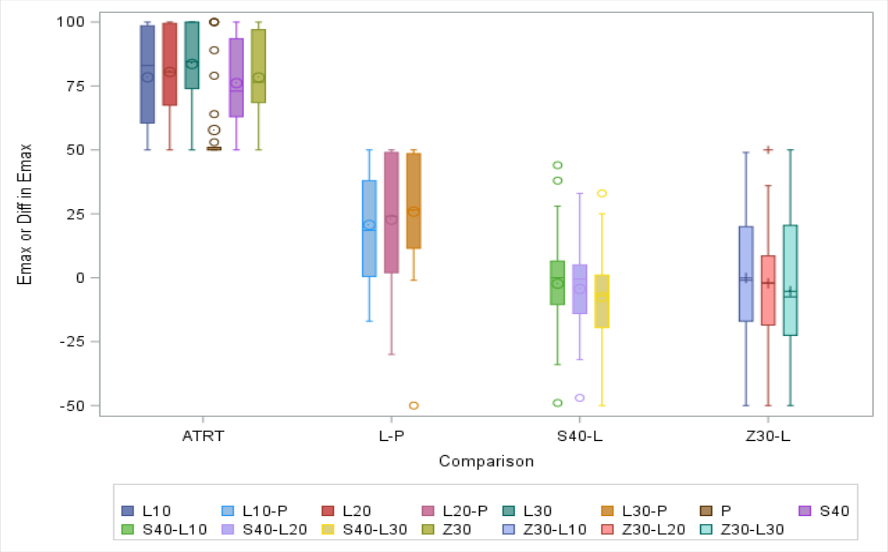


Figure 2: Boxplots for six treatments and the differences between treatments for Drug Liking Emax (N=32)

Figure 3 is the mean time course profiles by treatment for Drug Liking VAS

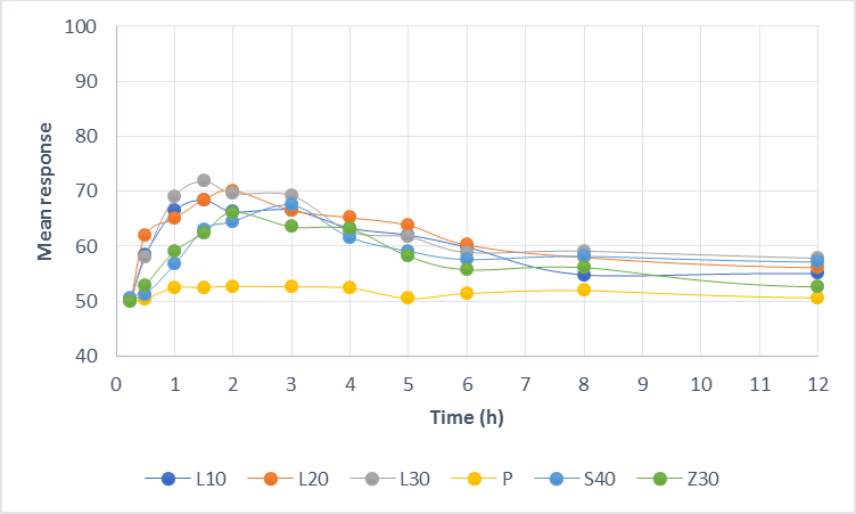


Figure 3: The mean time course response profiles in 12 hours by treatment for Drug Liking VAS (N=32)

Data for Drug Liking VAS were collected at hours 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24. To view clear picture of mean response profiles at early hours, the reviewer did not plot the mean at

hour 24. At hour 24, all treatments produced a mean response less than 55 except 40 mg suvorexant (57.1). Some subjects had missing responses at early hours for 30 mg zolpidem (See Figure 4). The mean response at a time point with missing responses was calculated based on observed data at the time point. The peak mean responses for 40 mg suvorexant and 30 mg zolpidem were 67.5 and 66.2, and the peak mean responses reached at hour 3 and 2, respectively. The peak mean responses for lemborexant 10 mg, 20 mg and 30 mg were 68.4, 70.1 and 71.8, respectively. The peak mean responses of lemborexant 10 mg and 30 mg reached at hour 1.5, while the time to peak mean response for lemborexant 20 mg was 2 hours post dose.

Figure 4 is the individual time course response profiles for 30 mg zolpidem in the Treatment Phase for Drug Liking VAS.

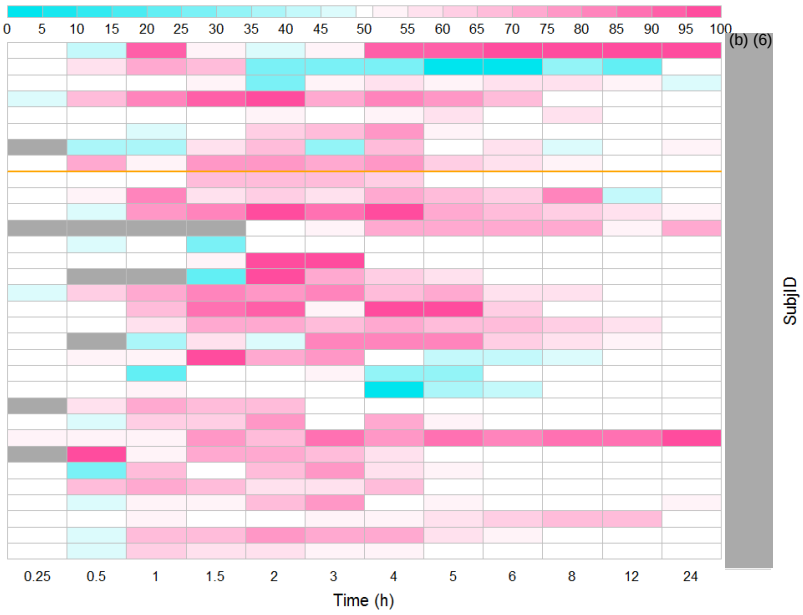


Figure 4: Individual time course response profiles for 30 mg zolpidem in the Treatment Phase for Drug Liking VAS (N=32)

The grey indicates missing responses. The reviewer examined the data from the Qualification Phase for the completers. None of the completers had any missing response for Drug Liking VAS for all treatment during the Qualification Phase. Figure 5 is the individual time course response profiles for 30 mg zolpidem in the Qualification Phase for Drug Liking VAS. One may see large differences in subjects' responses between the Treatment Phase and the Qualification Phase for 30 mg zolpidem.

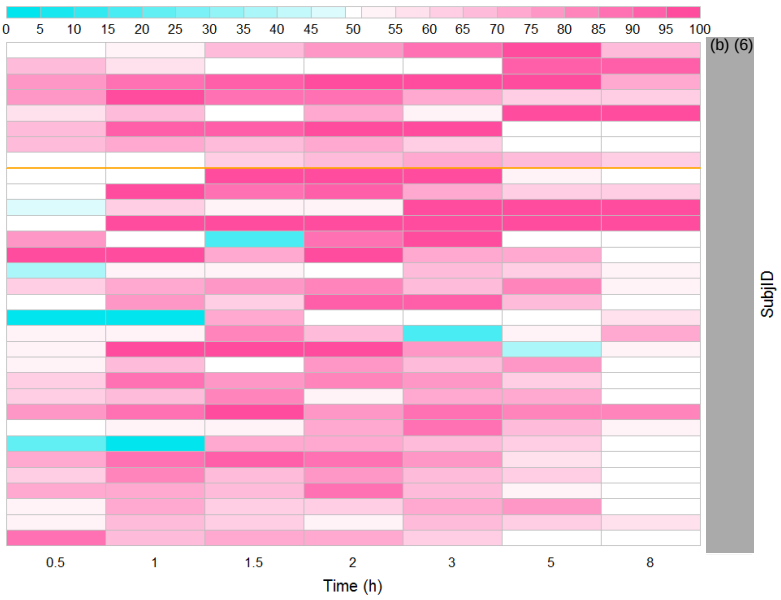


Figure 5: Individual time course response profiles for 30 mg zolpidem in the Qualification Phase for Drug Liking VAS (N=32)

2.3.1.2. Statistical Testing

To evaluate abuse potential of lemborexant, the following comparisons were performed for the primary endpoint, Drug Liking Emax.

1. S40 versus P		
2. Z30 versus P		
3. S40 versus L10	4. Z30 versus L10	5. L10 versus P
6. S40 versus L20	7. Z30 versus L20	8. L20 versus P
9. S40 versus L30	10. Z30 versus L30	11. L30 versus P

The comparisons #1 and #2 were for the study validation. The comparisons # 3, #4, #6, #7, #9 and #10 were for assessing the abuse potential of each dose of lemborexant relative to each of the positive controls. In the case that a dose of lemborexant did not have a statistically significantly lower mean response compared to either 40 mg suvorexant or 30 mg zolpidem, the comparison between lemborexant and placebo was not performed.

The statistical model used in the reviewer's primary analysis was a mixed-effects model which included sequence, period, treatment as fixed effects, and subject as a random effect, because the p-values of Levene test for homogeneity variances and the Shapiro-Wilk W-test for normality were 0.9062 and 0.2371, respectively, which indicated that the model assumptions were satisfied; and the p-value of carryover effect was 0.7825 (>0.25), the carryover effect was dropped from the model.

The FDA 2017 Guidance recommends the following hypotheses:

1. $H_0 : \mu_C - \mu_P \le \delta_1$ versus $H_a : \mu_C - \mu_P > \delta_1$,
2. $H_0 : \mu_C - \mu_T \le \delta_2$ versus $H_a : \mu_C - \mu_T > \delta_2$, and
3. $H_0 : \mu_T - \mu_P \ge \delta_3$ versus $H_a : \mu_T - \mu_P < \delta_3$,

where *C*, *T* and *P* denote suvorexant (or zolpidem), lemborexant and placebo, respectively. The sponsor pre-specified δ_1=15, δ_2 =0 and δ_3=11 were used in the reviewer's analysis.

Table 3 summarizes the least square means (LSMeans) by treatment.

Table 3: Least square means for Drug Liking Emax (N=32)

TRT	LSMean	StdErr	95% CI	
			LCL	UCL
L10	78.9	3.0	72.9	84.9
L20	80.9	3.0	74.9	86.9
L30	83.9	3.0	77.9	89.9
P	58.3	3.0	52.3	64.3
S40	76.5	3.0	70.5	82.5
Z30	78.5	3.0	72.5	84.5

The results from the primary analysis are listed in Table 3.

Table 4: Statistical analysis results for Drug Liking Emax (N=32)

Paired Comparison	Test Value	LSMean Diff	StdErr	P-value	95% CI	
					LCL	UCL
S40 vs P	15	18.2	3.7	0.1902	12.2	Infty
Z30 vs P	15	20.2	3.7	0.0787	14.1	Infty
S40 vs L10	0	-2.3	3.7	0.7372	-8.4	Infty
Z30 vs L10	0	-0.3	3.7	0.5376	-6.4	Infty
S40 vs L20	0	-4.3	3.7	0.8811	-10.4	Infty
Z30 vs L20	0	-2.4	3.7	0.7396	-8.4	Infty
S40 vs L30	0	-7.3	3.7	0.9767	-13.4	Infty
Z30 vs L30	0	-5.4	3.7	0.9277	-11.4	Infty

The validation tests for both 40 mg suvorexant and 30 mg zolpidem compared to placebo failed. However, the sponsor changed the test value to 11 after treatment unblinding. The sponsor's arguments were:

1. Although the original SAP was changed to comply with the FDA's request, the validation margin initially planned for the study was 11. The planned margin was identified on the basis of

published data defining clinically important differences in Drug Liking Emax in abuse potential studies (Schoedel et al., 2012).

2. In addition, the margin of 11 was purposefully selected to be less than the 15-point difference in maximum drug liking between the positive controls and placebo used for qualification purposes. A comparison of the maximum drug liking in response to an active comparator in the qualification versus treatment phases of a human abuse liability study has shown that during treatment subjects do not endorse drug liking at the same high levels as they do during the qualification period (Milovan et al., 2017).

In the Qualifications Phase, for Drug Liking Emax the means were 89.8, 89, and 50.4, and the standard deviations were 11.1, 11.1 and 0.6 produced by 40 mg suvorexant, 30 mg zolpidem and placebo, respectively. However, in the Treatment Phase, the means were 76.1, 78.3 and 57.8 and the standard deviations were 17.8, 16.0 and 16.2, produced by 40 mg suvorexant, 30 mg zolpidem and placebo, respectively. The smaller means and larger standard deviations from the Treatment Phase compared to those from Qualification Phase were due to 6 and 3 subjects who had a maximum liking score less than 55 for 40 mg suvorexant and 30 mg zolpidem, respectively; and 3 and 1 subjects who had maximum liking scores 100 and 89 for placebo, respectively.

The FDA 2017 Guidance states that the actual values of δ_1, δ_2, and δ_3 vary according to such factors as subjective measures, drug class, and route of drug administration.

In this reviewer's opinion, whether the δ_1 for the validation test must be greater than or equal to 15 for all schedule IV positive controls should be further investigated and should not be determined only by statisticians. However, the qualification procedure for selecting qualified subjects should be improved. It is important to put effort on preventing disqualified subjects from being selected to the Treatment Phase.

By using the test value 11 proposed by the sponsor, the p-values for the validation tests were 0.0251 (for S40 vs. P) and 0.0065 (for Z30 vs. P). Assume that the test value 11 for the validation test is acceptable, the reviewer's primary analysis showed that for Drug Liking Emax,

- both 40 mg suvorexant and 30 mg zolpidem produced LSMeans (76.5 and 78.5, respectively) significantly larger than placebo (58.3) by 11 points ($p \leq 0.0251$);
- none of the 3 lemborexant doses (10 mg, 20 mg and 30 mg) had a significantly smaller LSMean (78.9, 80.9 and 83.9, respectively) compared to either 40 mg suvorexant or 30 mg zolpidem ($p \geq 0.5376$). Note that the p-value of the comparison between 30 mg lemborexant and 40 mg suvorexant was 0.9767, which indicates that 30 mg lemborexant had a significantly larger LSMean compared to 40 mg suvorexant (p=1-0.9767=0.0233).

2.3.2. Secondary Analysis

The reviewer's secondary analysis included key secondary endpoints High Emax, Good Effects Emax, Overall Drug Liking Emax and Take Drug Again Emax. The descriptive statistics for Stoned Emax, Bad Effects Emax, Alertness/Drowsiness Emin and Any Effects Emax are presented in Appendix.

2.3.2.1. Descriptive Statistics

Figure 6 is the heat map by treatment for Good Effects Emax and High Emax.

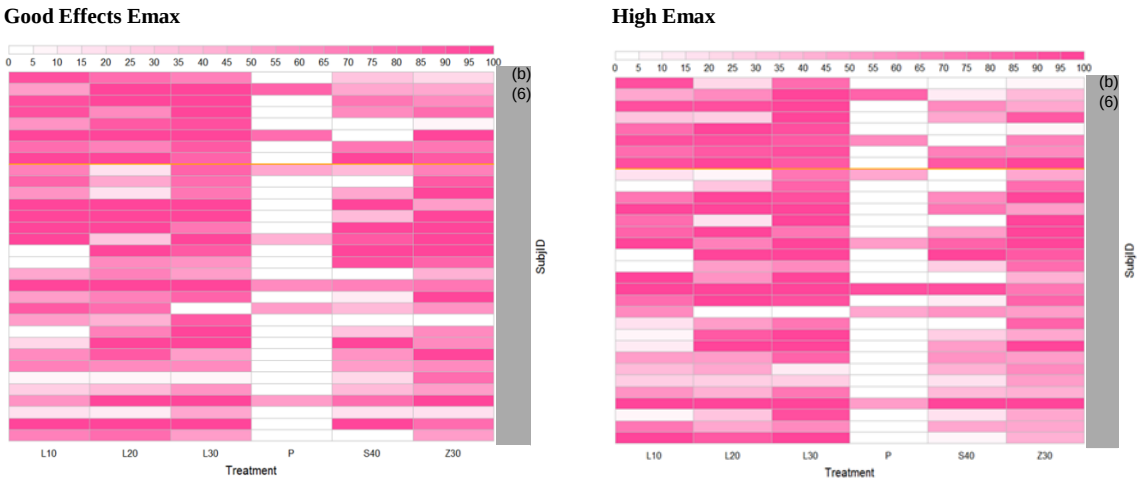


Figure 6: Heat map by treatment for Good Effects Emax and High Emax

Seven subjects (21.9%) had large maximum good effects and maximum high for the placebo. More subjects experienced high and good effects for 30 mg zolpidem compared to 40 mg suvorexant.

Figure 7 shows the heat map by treatment for Overall Drug Liking Emax and Take Drug Again Emax.

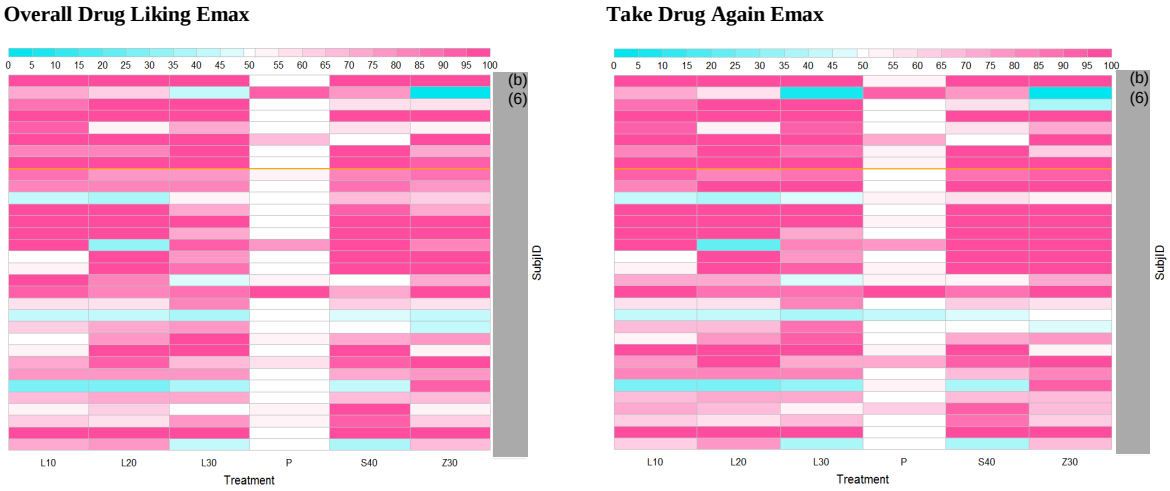


Figure 7: Heat map by treatment for Overall Drug Liking Emax and Take Drug Again Emax

Table 5 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for the key secondary endpoints Good Effects Emax, High Emax, Overall Drug Liking Emax and Take Drug Again Emax.

Table 5: Summary statistics for Good Effects Emax, High Emax, Overall Drug Liking Emax and Take Drug Again Emax (N=32)

Measure	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Good Effects VAS	L10	64.3	33.3	0	50.25	66.5	98	100
	L20	71.5	29.3	10	52	76.5	99	100
	L30	77.8	25.8	3	59.75	85	100	100
	P	13.6	25.8	0	0	1	2	85
	S40	50.9	35.7	0	19.25	49	87	100
	Z30	69.2	28.4	0	51.25	73	99	100
High VAS	L10	59.7	35.7	0	21.5	74	93	100
	L20	65.1	32.3	0	36.25	64.5	97	100
	L30	82.3	25.4	2	75	93	99.75	100
	P	14.0	27.3	-1	0	1	1	90
	S40	39.1	33.3	0	3.25	40.5	63	100
	Z30	65.3	26.1	6	47.25	63	87.75	100
Overall Drug Liking VAS	L10	76.6	22.5	25	53.75	80.5	99.75	100
	L20	78.2	22.9	26	62.5	82	99.75	100
	L30	77.3	21.0	35	68.25	79	98.75	100
	P	54.7	12.2	50	50	50	51	100
	S40	79.0	21.5	35	57.75	85	100	100
	Z30	75.6	23.3	0	60	78	98.75	100
Take Drug Again VAS	L10	78.2	21.6	25	62.75	82.5	100	100
	L20	79.8	23.6	23	62.5	86	100	100
	L30	78.2	24.8	9	70.25	86	100	100
	P	55.5	12.9	43	50	50	51	100
	S40	79.3	22.3	36	56.75	88	100	100
	Z30	78.7	24.7	0	61.5	87.5	100	100

The mean time course profiles by treatment for Good Effects VAS and High VAS, as well as bar plots for the mean responses at hours 12, 24 and 48 for Overall Drug Liking VAS and Take Drug Again VAS are presented in Figures 8 -11, respectively.

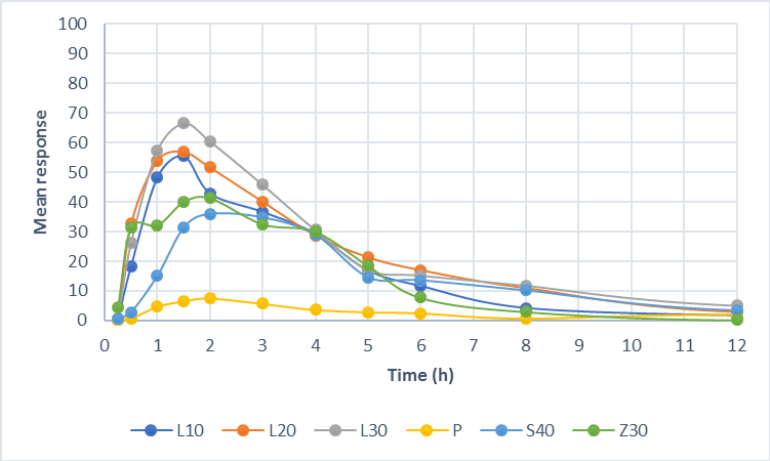


Figure 8: Mean Time Course Profiles by Treatment for Good Effects VAS (N=32)

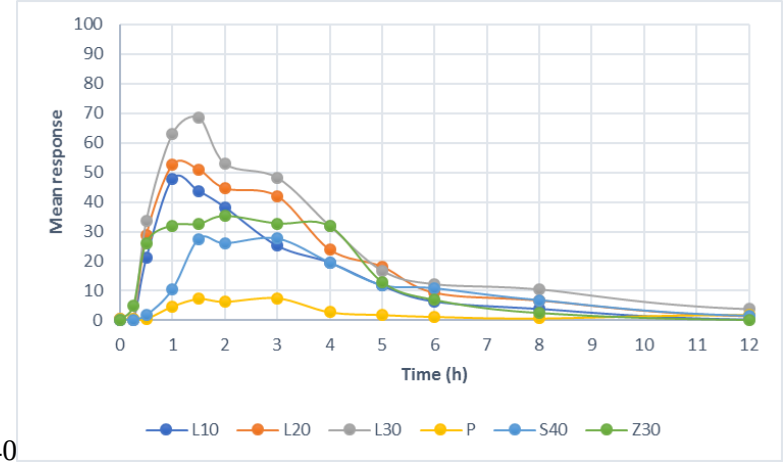


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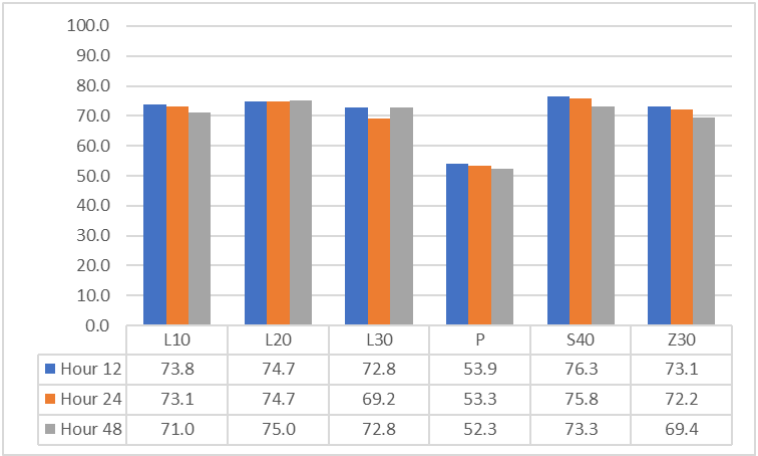
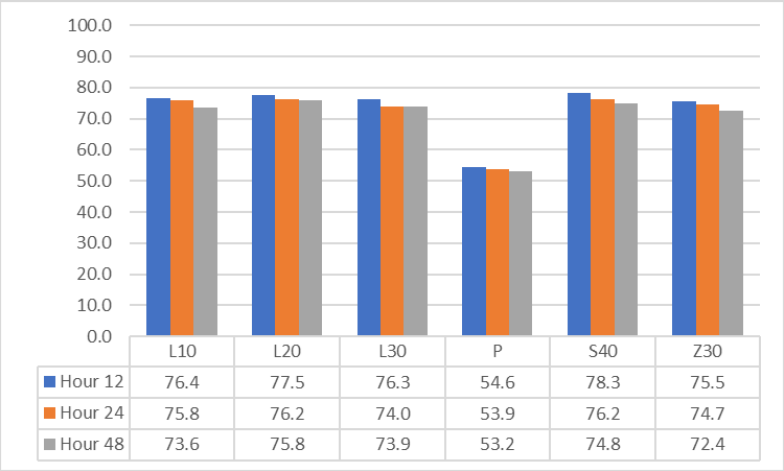
Figure 9: Mean Time Course Profiles by Treatment for High VAS (N=32)



	L10	L20	L30	P	S40	Z30
Hour 12	73.8	74.7	72.8	53.9	76.3	73.1
Hour 24	73.1	74.7	69.2	53.3	75.8	72.2
Hour 48	71.0	75.0	72.8	52.3	73.3	69.4

Figure 10: Bar Plot for mean responses of Overall Drug Liking VAS at Hours 12, 24 and 48 (N=32)



	L10	L20	L30	P	S40	Z30
Hour 12	76.4	77.5	76.3	54.6	78.3	75.5
Hour 24	75.8	76.2	74.0	53.9	76.2	74.7
Hour 48	73.6	75.8	73.9	53.2	74.8	72.4

Figure 10: Bar Plot for mean responses of Take Drug Again VAS at Hours 12, 24 and 48 (N=32)

The peak mean response for Good Effects VAS and High VAS produced by each dose of lemborexant was larger than both 40 mg suvorexant and 30 mg zolpidem. For Good Effects VAS the peak mean response produced by 30 mg lemborexant were 35.3 and 25.4 points larger compared to 40 mg suvorexant and 30 mg zolpidem, respectively. Similarly, for High VAS the peak mean response produced by 30 mg lemborexant were 40.8 and 33.3 points larger compared to 40 mg suvorexant and 30 mg zolpidem, respectively. For Good Effects VAS, all three doses of lemborexant reached the peak mean responses at hour 1.5, and both peak mean responses produced by 40 mg suvorexant and 30 mg zolpidem reached at hour 2.0. For High VAS the peak mean responses reached at hours 1.0, 1.0 and 1.5 for 10 mg, 20 mg and 30 mg lemborexant, and reached at hours 1.5 and 2.0 for 40 mg suvorexant and 30 mg zolpidem, respectively. For both Overall Drug Liking VAS and Take Drug Again VAS, no much difference among mean responses cross time and within each treatment or among active treatments would cause the reviewer's concern.

2.3.2.2. Statistical Testing

The statistical model prespecified for the secondary analysis was the mixed-effects model which included sequence, period, treatment, and carryover as fixed effects, and subject as a random effect. For High VAS, pre-dose response was also included in the model as a covariate. Table 6 shows that the normality assumption of the model was satisfied for Good Effects Emax and High Emax but not for Overall Drug Liking Emax and Take Drug Again Emax. Both Levene test and the test for the carryover effect were not significant (the nominal type I error rates were 0.05 and 0.25, respectively) for Good Effects Emax and High Emax. Therefore, for Good Effects Emax and High Emax the model did not include the carryover effect, and also did not need to adjust heteroscedasticity. For Overall Drug Liking Emax and Take Drug Again Emax the normality of the distribution of paired differences for each comparison was further examined.

Table 6: Results from the W test, Levene test, and the test for the carryover effects for Good Effects Emax, High Emax, Overall Drug Liking Emax, and Take Drug Again Emax (N=32)

Test	Good Effects	High	Overall Drug Liking	Take Drug Again
W	0.1271	0.6105	0.0051	0.0002
Levene	0.2071	0.1537		
Carryover	0.2535	0.2734		

Table 7 summarizes the least square means by treatment for Good Effects Emax and High Emax.

Table 7: Least square means for Good Effects Emax and High Emax (N=32)

Endpoint	TRT	LSMean	StdErr	95% CI	
				LCL	UCL
Good Effects Emax	L10	65.3	5.1	55.1	75.5
	L20	72.3	5.1	62.1	82.4
	L30	78.1	5.1	67.9	88.3
	P	14.5	5.1	4.3	24.6
	S40	51.5	5.1	41.3	61.7
	Z30	69.4	5.1	59.3	79.6
High Emax	L10	60.6	5.2	50.2	71.0
	L20	65.4	5.3	55.0	75.8
	L30	82.2	5.2	71.8	92.6
	P	14.6	5.3	4.2	25.0
	S40	39.7	5.3	29.3	50.1
	Z30	65.4	5.2	55.0	75.8

Table 8 lists the analysis results for Good Effects Emax and High Emax. The results show that: for Good Effect Emax and High Emax,

- the LSMeans produced by 40 mg suvorexant and 30 mg zolpidem were significantly larger than that produced by placebo by at least 15 points except the comparison between 40 mg suvorexant and placebo for High Emax, with the exception that the lower one-sided 95% confidence interval limit was 14.1, and the p-value was 0.0659. If the test value 11 was used, the test for this comparison would be significant;
  Reviewer's Comments: The study validity should be established on the primary endpoint(s). What test value should be used for the comparisons between positive control and placebo for secondary endpoints should be investigated.
- the p-values for the comparison between 40 mg suvorexant and each dose of lemborexant was at least 0.9822, which indicates all doses of lemborexant had significantly larger LSMeans compared to 40 mg suvorexant ($p \leq 1-0.9822=0.0178$);
- the LSMeans produced by 30 mg zolpidem were not significantly larger than any dose of lemborexant ($p \geq 0.2345$). Note that the p-value of the comparison between 30 mg zolpidem and

30 mg lemborexant for High Emax was 0.9939, which indicates LSMean produced by 30 mg lemborexant was significantly larger than that produced by 30 mg zolpidem (p=1-0.9939=0.0061) for High Emax.

Table 8: Analysis results for Good Effects Emax and High Emax (N=32)

Endpoint	Paired Comparison	Test Value	LSMean Diff	StdErr	P-value	95% CI	
						LCL	UCL
Good Effects Emax	S40 vs P	15	37.1	6.5	0.0004	26.3	Infty
	Z30 vs P	15	55.0	6.5	<.0001	44.2	Infty
	S40 vs L10	0	-13.8	6.5	0.9822	-24.5	Infty
	Z30 vs L10	0	4.2	6.5	0.2617	-6.6	Infty
	S40 vs L20	0	-20.7	6.5	0.9991	-31.5	Infty
	Z30 vs L20	0	-2.8	6.5	0.6671	-13.6	Infty
	S40 vs L30	0	-26.6	6.5	1.0000	-37.4	Infty
	Z30 vs L30	0	-8.7	6.5	0.9084	-19.4	Infty
High Emax	S40 vs P	15	25.1	6.7	0.0659	14.1	Infty
	Z30 vs P	15	50.8	6.6	<.0001	39.8	Infty
	S40 vs L10	0	-20.9	6.6	0.9990	-31.8	Infty
	Z30 vs L10	0	4.8	6.6	0.2345	-6.2	Infty
	S40 vs L20	0	-25.7	6.7	0.9999	-36.8	Infty
	Z30 vs L20	0	0.0	6.7	0.5021	-11.1	Infty
	S40 vs L30	0	-42.5	6.6	1.0000	-53.5	Infty
	Z30 vs L30	0	-16.8	6.6	0.9939	-27.8	Infty

According to the Amendment 2 of the SAP, if the normal assumption of the model was not satisfied, paired differences from each of the contrasts was tested. If the distribution of paired differences was normal ($p \geq 0.05$) or quite symmetric (skewness = –0.5 to 0.5), a t-test (adjusting for the margin) was used. If the distribution of the paired differences was not normal or quite symmetric, the Signed test was used. The Amendment 2 was made on the SAP after unblinding the study. Note that prespecified analysis was that if the paired differences were not normally distributed or quite symmetric, pairwise treatment comparisons would be assessed using the Wilcoxon signed-rank test on the within-subject differences, which was mistakenly suggested by the statistical reviewer at the Agency (See reviewer's comments on page 9 of this report). Therefore, even though the change on planned analysis was made after unblinding the study, it is acceptable.

Table 9 shows the results from the Shapiro-Wilk W test for Overall Drug Liking Emax and Take Drug Again Emax for paired comparisons. The p-values in red are greater than 0.05, and skewness in green are within -0.5 and 0.5. For these comparisons the t test was used. Otherwise, the Sign test was used (See the comparisons in purple). Again, if there was no significant mean or median difference between any of positive controls and a dose of lemborexant, the comparison between this dose of lemborexant and placebo was not performed.

Table 9: Results from the W Test on paired differences for Overall Drug Liking Emax and Take Drug Again Emax (N=32)

Endpoint	Comparison	Skewness	W Statistic	p-value
Overall Drug Liking Emax	S40-P	-0.50382	0.87441	0.00147
	Z30-P	-2.10006	0.80351	0.00005
	S40-L10	-0.08104	0.9438	0.09603
	Z30-L10	0.12315	0.90657	0.00914
	L10-P	-0.26859	0.91806	0.01842
	S40-L20	0.24425	0.90162	0.00681
	Z30-L20	0.26233	0.88014	0.00201
	L20-P	-0.97157	0.86687	0.00098
	S40-L30	-0.3113	0.96867	0.46355
	Z30-L30	0.02904	0.97568	0.66797
	L30-P	-0.98845	0.89399	0.00437
Take Drug Again Emax	S40-P	-0.31789	0.87319	0.00138
	Z30-P	-2.0503	0.79668	0.00004
	S40-L10	-0.03187	0.94996	0.14372
	Z30-L10	-0.15571	0.88046	0.00204
	L10-P	-0.33858	0.92414	0.02697
	S40-L20	0.65141	0.84894	0.00039
	Z30-L20	0.39076	0.79701	0.00004
	L20-P	-1.07124	0.85498	0.00053
	S40-L30	0.15579	0.9284	0.03534
	Z30-L30	-0.29499	0.9547	0.19567
	L30-P	-1.53423	0.82653	0.00013

Table 10 shows the results from reviewer's statistical analysis for Overall Drug Liking Emax and Take Drug Again Emax. The analysis results showed that for both Overall Drug Liking Emax and Take Drug Again Emax,

- except the comparison between 40 mg suvorexant and placebo for Take Drug Again Emax all other comparisons failed to demonstrate 15 points median difference between positive control and placebo. Based on the lower one-sided 95% confidence limits for these comparisons, if the test value was 10 instead of 15, all these tests would be significant (See reviewer's comments on page 23);
- none of the mean or median differences between each positive control and each dose of lemborexant was significantly greater than zero.

Table 10: Analysis results for Overall Drug Liking Emax and Take Drug Again Emax (N=32)

Endpoint	Paired Comparison	Test Value	Mean/Med Diff	StdErr/IQR	P-value	95% CI	
						LCL	UCL
Overall Drug Liking Emax	S40 vs P*	15	23.0	(-1, 47)	0.1725	13.0	Infty
	Z30 vs P*	15	21.0	(-1, 36)	0.2858	12.0	Infty
	S40 vs L10	0	1.0	3.8	0.3943	-5.4	Infty
	Z30 vs L10	0	-1.0	4.7	0.5839	-8.9	Infty
	S40 vs L20	0	0.8	4.2	0.4204	-6.2	Infty
	Z30 vs L20	0	-2.6	4.3	0.7220	-9.9	Infty
	S40 vs L30	0	1.8	3.7	0.3179	-4.5	Infty
	Z30 vs L30	0	-1.7	4.2	0.6536	-8.7	Infty
Take Drug Again Emax	S40 vs P	15	23.7	4.3	0.0258	16.4	Infty
	Z30 vs P*	15	23.0	(7, 33)	0.2025	10.0	Infty
	S40 vs L10	0	2.4	4.7	0.3057	-5.5	Infty
	Z30 vs L10	0	0.4	4.8	0.4643	-7.8	Infty
	S40 vs L20*	0	2.0	(-7, 13)	0.3233	-7.0	Infty
	Z30 vs L20	0	-1.2	4.8	0.5961	-9.4	Infty
	S40 vs L30	0	1.0	4.2	0.4033	-6.1	Infty
	Z30 vs L30	0	0.4	4.3	0.4601	-6.9	Infty

*: The Sign test was performed. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference were listed.
Note: Individual treatment mean, and standard are presented in Table 5.

3.3.3. Sensitivity Analysis

The reviewer did sensitivity analysis by eliminating subjects who had a negative difference between both positive controls and placebo (Subject ID (b) (6) The same statistical methodologies as those used in the primary analysis were used for the sensitivity analyses for the primary and key secondary endpoints. The test results are listed in Appendix II.

The sensitivity analysis on Drug Liking Emax showed that,

- both 40 mg suvorexant and 30 mg zolpidem produced LSMeans (78.2 and 78.8, respectively) significantly larger than placebo (55.0) by 15 points ($p \leq 0.0128$).
- both 40 mg suvorexant and 30 mg zolpidem did not have significantly larger LSMeans compared to the 3 lemborexant doses (78.2, 80.4, and 83.7 for 10 mg, 20 mg and 30 mg, respectively, $p \geq 0.4336$).

The sensitivity analysis on the key secondary endpoints showed that

- For High Emax, 40 mg suvorexant produced significantly smaller LSMean compared to each dose of lemborexant ($p \leq 0.0115$). The LSMean produced by 30 mg zolpidem was not significantly larger than those produced by 10 mg and 20 mg of lemborexant ($p \geq 0.1207$), and the LSMean produced by 30 mg zolpidem was significantly smaller compared to that produced by 30 mg lemborexant ($p = 0.0203$).
- For Good Effects Emax, 20 mg and 30 mg lemborexant produced mean were significantly larger than 40 mg suvorexant ($p \leq 0.0140$). The median difference between 40 mg suvorexant and 10 mg lemborexant was not significantly greater than zero ($p=0.9461$). Zolpidem 30 mg did not produce larger mean than each dose of lemborexant ($p \geq 0.2305$).
- None of the mean or median differences between each positive control and each dose of lemborexant was significantly greater than zero for Overall Drug Liking Emax and Take Drug Again Emax.

3. Conclusion

Because the primary analysis did not pass the validation test based on 32 completers, by using the test value 11 proposed by the sponsor, the reviewer performed analyses on primary endpoint Drug Liking Emax, as well as the four key secondary endpoints: Good Effects Emax, High Emax and Take Drug Again Emax. The reviewer also performed the sensitivity analysis by eliminating 3 subjects who had negative difference in maximum liking between both positive control and placebo. Based on the data from 29 subjects, both positive controls passed the validation test with the prespecified test value 15. The test results from the comparisons between positive controls and each dose of lemborexant based on 32 subjects and 29 subjects were the same for the primary and key secondary endpoints with an exception that LSMean produced by 40 mg suvorexant was significantly smaller than that produced by 30 mg lemborexant in the completers analysis for Drug Liking Emax but the difference was not significant in the sensitivity analysis.

Because both positive controls passed the validation tests with prespecified test value 15 for the primary endpoint in the sensitivity analysis, this reviewer summarized results from the sensitivity analyses in Table 11. For the primary endpoint and key secondary endpoints, the test results for the comparison between each positive control and each dose of lemborexant are listed. The NS and S denote that the test results are not significant and significant, respectively. S (<) denotes, for example, the mean produced by 40 mg suvorexant was significantly smaller than that produced by 10 mg lemborexant for Good Effects Emax. NS (>) denotes, for example, the mean of 30 zolpidem was larger than that of 20 mg lemborexant for High Emax, but not significantly larger. The mean difference between treatments with the standard error was also presented in the table for each of secondary endpoints under consideration.

Table 11: Summary of the results for the primary, key secondary and secondary endpoints considered in this review (N=29)

Study E2006-A001-103	Endpoint	Comparison	S40	Z30	P	L10	L20	L30
Primary	Drug Liking Emax	Mean (StdErr)	77.9 (3.2)	78.8 (3.1)	54.5 (2.4)	77.6 (3.5)	80.2 (3.4)	83.7 (3.0)
		S40 vs L				NS (=)	NS (<)	NS (<)
		Z30 vs L				NS (>)	NS (<)	NS (<)
Key Secondary	Good Effects Emax	Mean (StdErr)	54.4 (6.5)	69.7 (5.3)	9.3 (3.6)	64.1 (6.3)	69.6 (5.5)	77.2 (4.8)
		S40 vs L				S (<)	S (<)	S (<)
		Z30 vs L				NS (>)	NS (>)	NS (<)
	High Emax	Mean (StdErr)	42.9 (6.1)	67.2 (4.9)	10.7 (4.3)	57.8 (6.7)	65.0 (6.3)	81.3 (4.9)
		S40 vs L				S (<)	S (<)	S (<)
		Z30 vs L				NS (>)	NS (>)	S (<)
	Overall Drug Liking Emax	Mean (StdErr)	81.1 (3.9)	77.6 (3.6)	53.1 (1.9)	75.1 (4.2)	77.8 (4.4)	78.9 (3.7)
		S40 vs L				NS (>)	NS (>)	NS (>)
		Z30 vs L				NS (>)	NS (=)	NS (<)
	Take Drug Again Emax	Mean (StdErr)	81.3 (4.1)	80.9 (3.9)	53.9 (2.1)	77.7 (4.1)	80.1 (4.5)	81.0 (3.9)
		S40 vs L				NS (>)	NS (=)	NS (=)
		Z30 vs L				NS (>)	NS (=)	NS (<)
Secondary	Stoned Emax	Mean (StdErr)	33.1 (6.8)	57.7 (6.6)	7.6 (3.3)	44.8 (7.1)	51.7 (6.6)	62.0 (6.9)
		S40 vs L				-15.8 (7.4)	-22.2 (7.1)	-31.9 (6.5)
		Z30 vs L				12.8 (8.1)	6.3 (8.0)	-3.3 (8.2)
	Bad Effects Emax	Mean (StdErr)	12.4 (3.6)	40.6 (6.2)	5.7 (2.7)	24.2 (5.8)	34.1 (7.2)	40.6 (6.2)
		S40 vs L				-11.9 (5.0)	-21.4 (6.5)	-23.1 (6.2)
		Z30 vs L				15.7 (7.1)	6.2 (7.5)	4.5 (7.3)
	Alertness \Drowsiness Emin	Mean (StdErr)	14.6 (2.3)	14.9 (2.5)	41.8 (2.7)	8.3 (2.3)	6.8 (1.7)	5.9 (2.0)
		S40 vs L				7.8 (3.2)	9.6 (2.9)	10.5 (2.9)
		Z30 vs L				6.9 (2.7)	8.7 (2.4)	9.6 (3.2)
	Any Effects Emax	Mean (StdErr)	58.3 (6.4)	75.6 (6.9)	9.2 (3.9)	74.1 (6.4)	83.8 (4.0)	89.5 (2.8)
		S40 vs L				-20.5 (7.9)	-27.5 (5.7)	-33.0 (5.8)
		Z30 vs L				-1.9 (7.3)	-9.1 (5.2)	-14.4 (5.1)

None of the two positive controls produced significantly larger maximum liking compared to each dose of lemborexant. All doses of lemborexant procedure significantly larger good effects and high compared to 40 mg suvorexant. The 30 mg lemborexant also produced significantly larger high compared to 30 zolpidem. No significant difference between each positive control and each dose of lemborexant was found in other comparisons for key secondary endpoints. For the secondary endpoints considered in this review, lemborexant showed larger stoned and larger bad effects compared to suvorexant and larger any effects compared to both 40 mg suvorexant and zolpidem. The means of Alertness/Drowsiness Emin produced by all doses of lemborexant were smaller than those produced by 40 mg suvorexant and 30 mg zolpidem.

In conclusion, the abuse potential of lemborexant may be similar to zolpidem but larger than suvorexant.

4. Appendix I

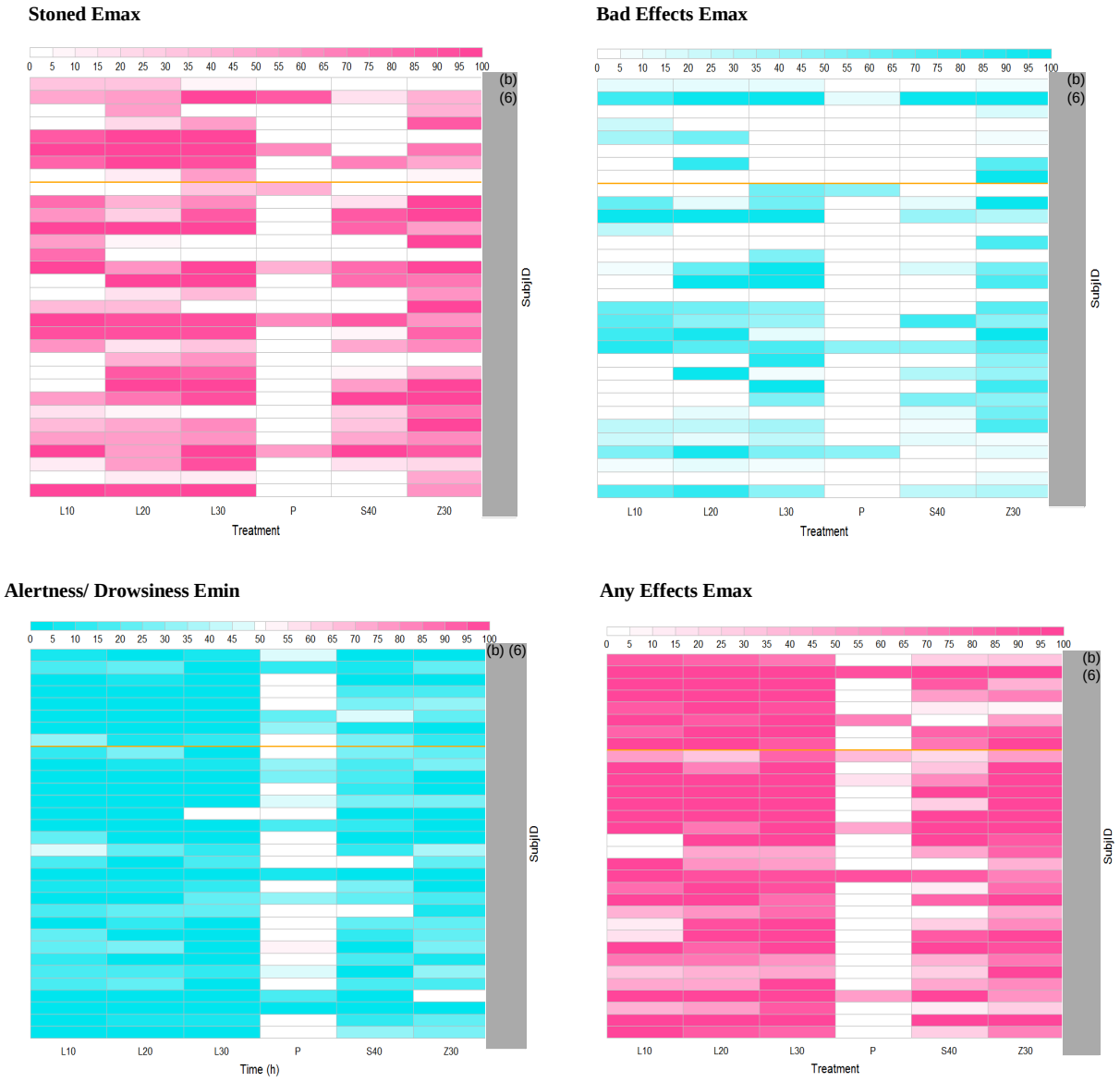


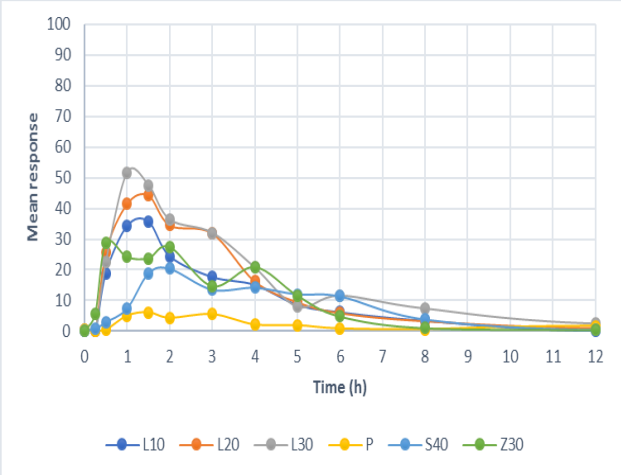
Figure 11: Heat Map by Treatment for Stoned Emax, Bad Effects Emax, Alertness/Drowsiness Emin, and Any Effects Emax (N=32)

Note that for Alertness/Drowsiness VAS, many subjects had neutral score at the baseline. It results in many negative changes from per-dose responses. Therefore, heat maps for Stone Emax and Alertness/Drowsiness Emin were based on post dose observations, not change from baseline observations.

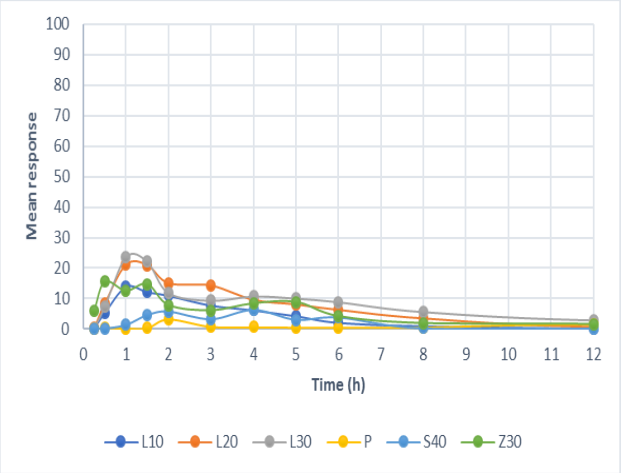
Table 12: Descriptive Statistics for Stoned Emax, Bad Effects Emax, Alertness/Drowsiness Emin, and Any Effects Emax

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Stoned Emax	L10	46.4	39.2	0	1	49.5	87	100
	L20	52.8	34.8	0	17.75	51	94.75	100
	L30	62.5	38.4	0	31	74.5	97	100
	P	11.6	24.1	0	0	1	2	87
	S40	30.6	35.7	0	1	13.5	63.5	100
	Z30	59.1	34.8	0	41.5	61.5	94.5	100
Bad Effects Emax	L10	26.3	32.2	0	1	9.5	58.5	100
	L20	35.8	39.3	0	1.25	12.5	78.25	100
	L30	37.5	36.9	0	2	31.5	59	100
	P	5.5	13.8	0	0	1	2	49
	S40	14.4	24.4	0	0	1	18	100
	Z30	42.0	34.5	0	6.5	45.5	71.5	100
Alertness \Drowsiness Emin	L10	8.6	11.8	0	0	2	16.5	49
	L20	6.9	9.3	0	0	2	10.5	29
	L30	6.0	10.4	0	0	1.5	9.5	50
	P	40.4	15.5	1	33	50	50	51
	S40	16.4	14.3	0	3	14.5	26.75	50
	Z30	15.5	13.1	0	2.25	16	24.75	50
Any Effects Emax	L10	76.5	33.4	0	50.25	97.5	100	100
	L20	83.6	21.1	35	67.5	95.5	100	100
	L30	89.0	16.0	49	83.25	96	100	100
	P	13.3	26.9	0	0	1	3.75	92
	S40	56.0	36.4	0	26.25	52	96	100
	Z30	74.6	26.6	7	55.25	81.5	99.75	100

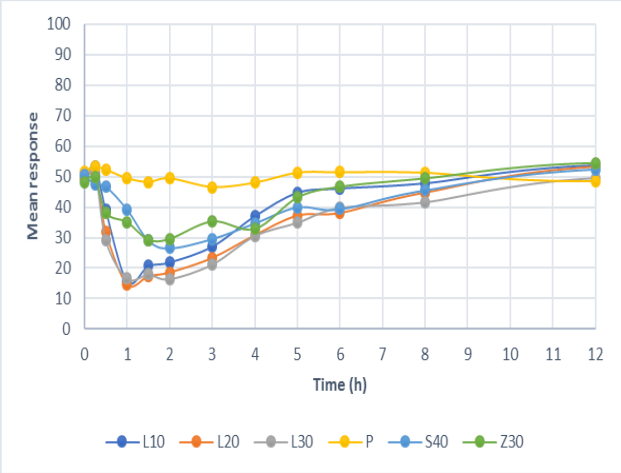
Stoned VAS



Bad Effects VAS



Alertness/Drowsiness VAS



Any Effects VAS

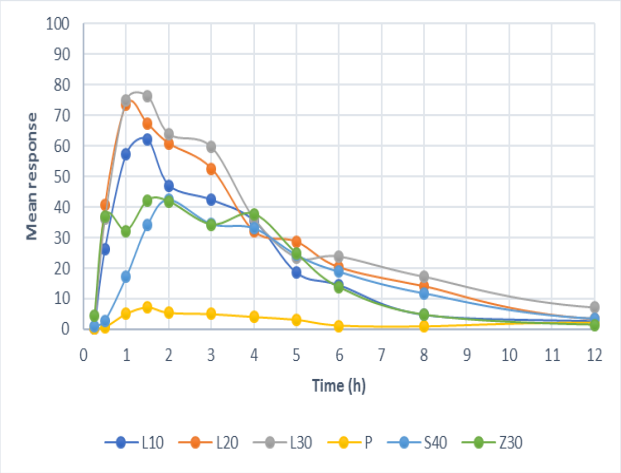


Figure 12: The mean time course response profiles in 12 hours on Stoned VAS, Bad Effects VAS, Alertness/Drowsiness VAS and Any Effects VAS by treatment (N=32)

5. Appendix II

Table 13: Summary statistics for Drug Liking Emax (N=29)

TRT	Mean	SD	Min	Q1	Med	Q3	Max
L10	77.6	19.0	50	58	83	98.5	100
L20	80.2	18.3	50	64.5	82	100	100
L30	83.7	16.2	50	74	83	100	100
P	54.5	12.9	50	50	51	51	100
S40	77.9	17.4	50	65.5	76	96.5	100
Z30	78.8	16.7	50	66.5	77	98	100

Table 14: Least square means for Drug Liking Emax (N=29)

TRT	LSMean	StdErr	95% CI	
			LCL	UCL
L10	78.2	3.1	72.0	84.4
L20	80.4	3.1	74.2	86.7
L30	83.7	3.1	77.5	89.9
P	55.0	3.1	48.8	61.3
S40	78.2	3.1	71.9	84.4
Z30	78.8	3.1	72.6	85.0

Table 15: Statistical analysis results for Drug Liking Emax (N=29)

Paired Comparison	Test Value	LSMean Diff	StdErr	P-value	95% CI	
					LCL	UCL
S40 vs P	15	23.1	3.6	0.0128	17.2	Infty
Z30 vs P	15	23.8	3.6	0.0081	17.8	Infty
S40 vs L10	0	0.0	3.6	0.5047	-6.0	Infty
Z30 vs L10	0	0.6	3.6	0.4336	-5.4	Infty
S40 vs L20	0	-2.3	3.6	0.7354	-8.2	Infty
Z30 vs L20	0	-1.6	3.6	0.6740	-7.6	Infty
S40 vs L30	0	-5.5	3.6	0.9372	-11.5	Infty
Z30 vs L30	0	-4.9	3.6	0.9124	-10.8	Infty

Table 16: Summary statistics for Good Effects Emax, High Emax, Overall Drug Liking Emax and Take Drug Again Emax (N=29)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Good Effects Emax	L10	64.1	34.2	0	40.5	67	97	100
	L20	69.6	29.8	10	46.5	76	98.5	100
	L30	77.2	26.0	3	60.5	84	99.5	100
	P	9.3	19.6	0	0	1	2	62
	S40	54.4	34.9	0	27.5	53	92.5	100
	Z30	69.9	28.6	0	56	74	99	100
High Emax	L10	57.8	36.2	0	18.5	74	93.5	100
	L20	65.0	33.7	0	34	68	100	100
	L30	81.3	26.3	2	74.5	92	100	100
	P	10.7	23.3	0	0	1	2	92
	S40	42.9	32.8	0	11	48	65.5	100
	Z30	67.2	26.4	6	49.5	65	92	100
Overall Drug Liking Emax	L10	75.1	22.8	25	52	77	99	100
	L20	77.8	23.5	26	61	81	99.5	100
	L30	78.9	19.7	35	72.5	79	99	100
	P	53.1	10.4	50	50	50	50.5	100
	S40	81.1	21.1	35	64.5	92	100	100
	Z30	77.6	19.4	44	61	80	99	100
Take Drug Again Emax	L10	77.7	22.3	25	61	83	100	100
	L20	80.1	24.2	23	64.5	87	100	100
	L30	81.0	21.2	32	72	86	100	100
	P	53.9	11.3	43	50	50	51	100
	S40	81.3	22.0	36	61	92	100	100
	Z30	80.9	20.8	38	62	92	100	100

Table 17: Analysis results for Good Effects Emax, High Emax, Overall Drug Liking Emax and Take Drug Again Emax (N=29)

Endpoint	Paired Comparison	Test Value	Mean/Med Diff	StdErr/IQR	P-value	95% CI	
						LCL	UCL
Good Effects Emax	S40 vs L10*	0	-9.0	(-40, 0)	0.9461	-30.0	Infty
	Z30 vs L10	0	5.8	7.7	0.2305	-7.4	Infty
	S40 vs L20*	0	-3.0	(-3, 32)	0.9860	-38.0	Infty
	Z30 vs L20	0	0.2	7.0	0.4864	-11.7	Infty
	S40 vs L30	0	-22.8	6.7	0.9990	-34.1	Infty
	Z30 vs L30	0	-7.3	6.7	0.8585	-18.8	Infty
High Emax	S40 vs L10	0	-15.7	6.8	0.9885	-27.0	Infty
	Z30 vs L10	0	8.0	6.9	0.1207	-3.3	Infty
	S40 vs L20	0	-22.0	6.9	0.9991	-33.4	Infty
	Z30 vs L20	0	1.7	6.9	0.4012	-9.7	Infty
	S40 vs L30	0	-37.9	6.9	1.0000	-49.3	Infty
	Z30 vs L30	0	-14.1	6.8	0.9797	-25.5	Infty
Overall Drug Liking Emax	S40 vs L10*	0	1.0	(-5, 20)	0.0999	0.0	Infty
	Z30 vs L10	0	2.5	4.3	0.2829	-4.9	Infty
	S40 vs L20*	0	1.0	(-2, 5)	0.4149	0.0	Infty
	Z30 vs L20*	0	0.0	(-7, 3)	0.3882	-3.0	Infty
	S40 vs L30	0	2.2	3.5	0.7391	-3.6	Infty
	Z30 vs L30	0	-1.3	4.3	0.6196	-8.6	Infty
Take Drug Again Emax	S40 vs L10	0	3.6	3.7	0.3335	-2.6	Infty
	Z30 vs L10	0	3.2	4.6	0.2501	20.6	Infty
	S40 vs L20*	0	0.0	(-1. 2)	0.3745	0.0	Infty
	Z30 vs L20*	0	0.0	(-2, 2)	0.3451	0.0	Infty
	S40 vs L30*	0	0.0	(-1, 10)	0.3311	0.0	Infty
	Z30 vs L30	0	-0.1	4.7	0.5088	-8.1	Infty

*: The Sign test was performed. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference were listed.
Note: Individual treatment mean, and standard are presented in Table 16.

Table 18: Summary statistics for Any Effects Emax, Bad Effects Emax, Alertness/Drowsiness Emax and Stoned Emax (N=29)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Any Effects Emax	L10	74.1	34.3	0	47	96	100	100
	L20	83.8	21.3	35	69	97	100	100
	L30	89.5	15.3	49	83.5	96	100	100
	P	9.2	21.2	0	0	1	2.5	92
	S40	58.3	34.2	0	27	54	94	100
	Z30	75.6	26.5	7	59	85	99.5	100
Bad Effects Emax	L10	24.2	31.3	0	0.5	9	44.5	100
	L20	34.1	38.7	0	1.5	12	74.5	100
	L30	36.1	36.3	0	2	27	59	100
	P	5.7	14.5	0	0	1	2	49
	S40	12.4	19.4	0	0	1	17	76
	Z30	40.6	33.4	0	7	45	71	100
Alertness / Drowsiness Emax	L10	8.3	12.1	0	0	1	16	49
	L20	6.8	9.3	0	0	1	10	29
	L30	5.9	10.6	0	0	2	9	50
	P	41.8	14.7	1	33.5	50	50	51
	S40	14.6	12.3	0	2	14	24.5	50
	Z30	14.9	13.6	0	2	15	25	50
Stoned Emax	L10	44.8	40.0	0	1	51	86	100
	L20	51.7	35.5	0	16	51	94.5	100
	L30	62.0	37.3	0	31	64	96	100
	P	7.6	17.8	0	0	1	2	63
	S40	33.1	36.5	0	1	18	73	100
	Z30	57.7	35.5	0	31.5	60	93	100

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LING CHEN
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 212028
Drug Name:	E2006; lemborexant
Indication:	Treatment of insomnia disorder
Applicant:	Eisai Co., Ltd. 155 Tile Blvd, Woodcliff Lake, NJ 07677 Test Facility for Rats and mice Studies: (b) (4) [redacted]
Documents Reviewed:	Study reports (Study K13092 and K15016)and Electronic data submitted on March 1, 2017 via IND111871/Sequence 0105
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Zhuang Miao, Ph.D.
Concurring Reviewer:	Feng Zhou, MS Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	Avila, Amy, Ph.D.
Project Manager:	Kiedrow, Keith
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1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague-dawley rats and one in CB6F1-Tg rasH2 mice. These studies were intended to assess the carcinogenic potential of E2006 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: Three hundred Sprague Dawley rats of each sex were randomly assigned to the three treated and two vehicle control groups in equal size of 60 rats per group. The dose levels for treated groups in male rats were 30, 100, and 300 mg/kg/day. The dose levels for treated groups in female rats were 10, 30 and 100 mg/kg/day. The rats in the vehicle control groups received the vehicle(0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid [4:1, v/v]). The study for the rats was designed to continue for up to 104 weeks; and all surviving male rats were sacrificed during Week 105.

The survival analyses did not show a statistically significant dose response relationship in mortality across the combined vehicle control group and treated groups for either males or females. The pairwise comparisons did not show statistically significant differences in mortality between the combined vehicle control group and each of the treated groups for either males or females, except the differences between the combined vehicle control group and the 10 mg/kg/day group in females. However, the difference between the combined vehicle control group and the 10mg/kg/day group is a negative finding.

The tumor analysis did not show any tumor types with a statistically significant positive dose response in either males or females. The pairwise comparisons did not show statistically significant increases in incidence in any observed tumor types in any treated groups in either males or females.

Mouse Study: One hundred CB6F1-Tg rasH2 mice of each sex were randomly assigned to the three treated and vehicle control group in equal size of 25 mice per group. There were 15 mice of each sex in the positive control group. The dose levels for treated groups were 50, 150, and 500 mg/kg/day. The mice in the vehicle control group received the vehicle (0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid (4:1, v/v)). The study was designed to continue for up to 26 weeks for both sexes and all surviving mice were sacrificed during Week 27. The mice in the positive control group received a single intraperitoneal injection of N-nitroso-N-methylurea (MNU) at 75 mg/kg on Day 1. Positive control animals were sacrificed on Day 134 (males) or Day 154 (females).

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control and each of the treated groups for either males or females.

The pairwise comparisons between the vehicle control group and the positive control group showed a statistically significant increase in mortality in the positive control group for both the male and female mice.

The trend test showed a statistically significant positive dose response relationship in incidence of hemangiosarcoma in spleen (p-value=0.0129<0.05) and the combined tumors of hemangiosarcoma and hemangioma in the whole body (p-value=0.0205<0.05) between the vehicle control and the treated groups in male mice

The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of malignant lymphoma in hematophoietic (p-value<0.001), forestomach papilloma in stomach (p-value<0.001) and squamous cell carcinoma in stomach (p-value=0.0017<0.05) in male mice; malignant lymphoma in hematophoietic (p-value<0.001), papilloma in skin (p-value<0.001) and forestomach

papilloma in stomach (p-value<0.001) in female mice.

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague-dawley rats and one in CB6F1-Tg rasH2 mice. These studies were intended to assess the carcinogenic potential of E2006 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Avila. This review analyzed the SAS data sets of these studies received from the sponsor on March 1, 2017 via IND111871/Sequence 0105.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two vehicle control groups. Three hundred Sprague Dawley rats of each sex were randomly assigned to the three treated and the two vehicle control groups in equal size of 60 rats per group. The dose levels for treated groups in male rats were 30, 100, and 300 mg/kg/day. The dose levels for treated groups in female rats were 10, 30 and 100 mg/kg/day. The rats in the vehicle control group received the vehicle(0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid [4:1, v/v]). The study for the rats was designed to continue for up to 104 weeks, and all surviving male rats were sacrificed during Week 105.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Identical Vehicle	60	60
2	0	Identical Vehicle	60	60
3	10	E2006		60
4	30	E2006	60	60
5	100	E2006	60	60
6	300	E2006	60	

3.1. Sponsor's analyses

3.1.1. Survival analysis

For survival rate analysis, the survival curves (Kaplan-Meier's curves) for individual groups were estimated by Kaplan-Meier's method (product limit estimator) (Kaplan and Meier, 1958). Survival rates in the Control-1 and Control-2 groups were analyzed by log-lank test. Then, when there were no significant differences, the combined control group (combination of the Control-1 and Control-2 groups) was treated as the substantive control group and the following analysis was conducted. When there were some significant differences, the Control-1, Control-2 and combined control groups were treated as the independent control groups and the following analysis was conducted. The decreased trend of survival rate to dose level was analyzed by Tarone-type method, and then the differences between the control group and each dose group were compared using log-rank test. Tarone-type method and log-rank test were conducted at a significance level of 5% in upper probability level.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of death were 15 (25%), 18 (30%), 13 (47%), 20 (33.3%) and 17 (28.3%) in vehicle control 1, vehicle control 2, 30 mg/kg/day, 100 mg/kg/day and 300 mg/kg/day dose groups, respectively in males and 15 (25%), 17 (28.3%), 7 (11.7%), 9 (15%) and 9

(15%) in vehicle control 1, vehicle control 2, 10 mg/kg/day, 30 mg/kg/day and 100 mg/kg/day dose groups, respectively in females.

The sponsor made the following conclusions: there was no significantly decreased trend on the survival rate related to dose level in males or females.

3.1.2. Tumor data analysis

For tumor incidence analysis, Fisher's exact test was applied for all tumors to assess the differences of tumor incidence between the Control-1 and Control-2 groups. Then, when there were no significant differences, the combined control group (combination of the Control-1 and Control-2 groups) was treated as the substantive control group and the following analysis was conducted. When there were some significant differences, the Control-1, the Control-2 and the combined control groups were treated as the independent control groups and the following analysis was conducted. The above test was conducted at a significance level of 5% in two-tailed level. High incidence tumors (10 animals or more animals per sex) were analyzed by the survival-adjusted Peto's mortality-prevalence method to assess an increasing trend of incidence to dose level for all groups (positive trend), and to compare the incidence between the each control group and each dose group (pairwise comparison). Low incidence tumors (less than 10 animals per sex) were analyzed by Peto's exact permutation test to assess for analyzing positive trend and pairwise comparison. In the incidental tumor analysis, the fixed intervals were defined as follows: Weeks 1-50, 51-80, 81-104 and scheduled terminal sacrifice. Significance level for analyzing positive trend was 1% in one-tailed level for common tumors and 5% in one-tailed level for rare tumors, and for pairwise comparison was 5% in one-tailed level for both common and rare tumors. Common tumors were defined as those exceeding 1% (>1%) and rare tumors as 1% or less (≤1%) in the historical background data at (b) (4) (Mary and Charles, 2004).

Sponsor's findings: The sponsor's analyses did not show a statistically significant dose response relationship among the treated and vehicle groups in any of the observed tumor types in male or female rats.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on March 1, 2017 via IND111871/Sequence 0105. Note that, in the submitted tumor data, the two identical vehicle control groups were combined. Therefore, all statistical comparisons were between combined vehicle control group and treated groups."

3.2.1. Survival analysis

The survival distributions of animals in all four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for combined vehicle control, low, medium, and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 7 and 8 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 9 and 10 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death were 33 (27.5%), 13 (21.67%), 20 (33.3%), and 17 (28.3%) in male rats for the combined vehicle control group, 30 mg/kg/day, 100

mg/kg/day and 300 mg/kg/day groups respectively; and 32 (26.7%), 7 (11.67.%), 9 (15%), and 9 (15%) in female rats for the combined vehicle control group, 10 mg/kg/day, 30 mg/kg/day and 100 mg/kg/day groups, respectively.

The survival analyses did not show a statistically significant positive dose response relationship in mortality across combined vehicle control group and treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the combined vehicle control groupo and each of the treated groups for either males or females except the differences between the combined vehicle control group and the 10 mg/kg/day group in females. However, the difference between the combined vehicle control group and the 10mg/kg/day group is a negative finding.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 11 and 12 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels α =0.005 for common tumors and α=0.025 for rare tumors for the chronic rat study. For pairwise comparisonsfor the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels α =0.01 for common tumors and α =0.05 for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either in tests for dose response relationship or in pairwise comparisons between the vehicle control group and each of the the treated groups.

Table 2: Tumor Types with P-Values ⩽ 0.05 for Dose Response Relationship or Pairwise Comparisons between Combined Vehicle Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-Value Trend	30 mg/kg/day Low (N=60) P-Value - Combined Vehicle vs. Low	100 mg/kg/day Med (N=60) P-Value – Combined Vehicle vs. Medium	300 mg/kg/day High (N=60) P-Value - Combined Vehicle vs. High
HEMATOPOIETIC AND	HISTIOCYTIC SARCOMA	1/120 (109) 0.0415	1/60 (56) 0.5650	0/60 (52) 1.0000	3/60 (53) 0.1030

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Reviewer's findings: Based on the above criterion for multiple testing adjustment, we make the folloing conclusions: (1) No tumor types had a statistically significant positive dose response in either males or females. (2) The pairwise comparisons did not show any statistically significant increases in incidence for any observed tumor types in any treated groups in either males or females when compared with the combined vehicle control group.

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred CB6F1-Tg rasH2 mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There were 15 mice of each sex in the positive control group. The dose levels for treated groups were 50, 150, and 500 mg/kg/day. The mice in the vehicle control group received the vehicle (0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid (4:1, v/v)). The study was designed to continue for up to 26 weeks for both sexes and all surviving mice were sacrificed during Week 27. The mice in the positive control group received a single intraperitoneal injection of N-nitroso-N-methylurea (MNU) at 75 mg/kg on Day 1. Positive control animals were sacrificed on Day 134 (males) or Day 154 (females).

Table 3: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	25	25
2	50	Low Dose	25	25
3	150	Middle Dose	25	25
4	500	High Dose	25	25
5	MNU: 75	Positive	15	15

4.1. Sponsor's analyses

4.1.1. Survival analysis

The sponsor used the same survival analysis methods used for the rats study in this mouse study.

Sponsor's findings: The sponsor's analysis showed 1 (4%), 0 (0%), 0 (0%), 2 (8%), and 7 (46.6%) mortalities in male mice, and 0 (0%), 2 (8%), 2 (8%), 0 (0%), and 6 (40%) mortalities in female mice in vehicol control, low, medium, high dose groups, and positive control group, respectively.

There were no statistically significant differences in survival rates in either males or females at any dosed groups.

4.1.2. Tumor data analysis

The sponsor used the same tumor data analysis methods used for the rat study in this mouse study

Sponsor's findings: The sponsor's trend tests showed that there were statistically significant increases in incidenc of hemangiosarcoma in the spleen (p-value=0.0132) and hemangiosarcoma (p-value=0.0029) and hemangiosarcoma/hemangioma in the whole body (p-value=0.0203) in male mice.

4.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, the reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on March 1, 2017 via IND111871/Sequence 0105. The significance level for all statistical tests was set at 0.05.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 13 and 14 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the vehicle control and three treated groups are given in Tables 15 and 16 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death were 1 (4%), 0 (0%), 0 (0%), 2 (8%), and 7 (46.6%) in male mice 0 (0%), 2 (8%), 2 (8%), 0 (0%), and 6 (40) in female mice in the vehicle control group, 50 mg/kg/day, 150 mg/kg/day, 500 mg/kg/day groups, and positive control group, respectively.

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups for either males or females. The pairwise comparisons did not show statistically significant differences in mortality between the vehicle control and each of the treated groups for either males or females.

The pairwise comparisons showed a statistically significant increase in mortality in the positive control group when compared to the vehicle control for both the male and female mice. The p-values for Likelihood Ratio test were <0.0001 and <0.0001 and the p-values for Log-Rank test were <0.0001 and <0.0001, respectively for male and female mice.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the rat study in this mouse study

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and three treated groups, vehicle control and positive control are listed in Tables 17, 18, 19 and 20 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels α =0.05 for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels α =0.05 for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 for pairwise comparisons between the vehicle control group and the treated groups and between the vehicle control goup and the positive control group.

Table 4: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and the Treated Groups -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	150 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	500 mg/kg/day High (N=25) P-value - Vehicle vs. High
SPLEEN	HEMANGIOSARCOMA	0/25 (25) 0.0129	0/25 (25) NC	0/25 (25) NC	3/25 (24) 0.1099
Whole Body	C_Hemangiosarcoma+hemangioma	0/25 (25) 0.0205	2/25 (25) 0.2449	0/25 (25) NC	4/25 (24) 0.0502

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 5: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	MNU: 75 Positive (N=15) P-value - Vehicle vs. Positive
HEMATOPOIETIC AND	MALIGNANT LYMPHOMA	0/25 (25)	10/15 (11) <0.001
STOMACH	PAPILLOMA, FORESTOMACH	0/25 (25)	11/15 (12) <0.001
	SQUAMOUS CELL CARCINOMA	0/25 (25)	4/15 (8) 0.0017

Table 6: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value	MNU: 75 Positive (N=15) P-value - Vehicle vs. Positive
HEMATOPOIETIC AND	MALIGNANT LYMPHOMA	0/25 (25)	9/15 (12) <0.001
SKIN	PAPILLOMA	0/25 (25)	6/15 (10) <0.001
STOMACH	PAPILLOMA, FORESTOMACH	0/25 (25)	14/15 (14) <0.001

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following conclusions:

1. The tumor data analysis showed a statistically significant positive dose response relationship in incidence of hemangiosarcoma in spleen (p-value=0.0129<0.05) and in combined tumors of hemangiosarcoma and hemangioma in the whole body (p-value=0.0205<0.05) between the vehicle control and the treated groups in male mice
2. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of malignant lymphoma in hematophoietic (p-value<0.001), forestomach papilloma in stomach (p-value<0.001) and squamous cell carcinoma in stomach (p-value=0.0017<0.05) in male mice; malignant lymphoma in hematophoietic (p-value<0.001), papilloma in skin (p-value<0.001) and forestomach papilloma in stomach (p-value<0.001) in female mice.

5. Conclusion

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague-dawley rats and one in CB6F1-Tg rasH2 mice. These studies were intended to assess the carcinogenic potential of E2006 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: Three hundred Sprague Dawley rats of each sex were randomly assigned to the three treated and the two vehicle control groups in equal size of 60 rats per group. The dose levels for treated groups in male rats were 30, 100, and 300 mg/kg/day. The dose levels for treated groups in female rats were 10, 30 and 100 mg/kg/day. The rats in the vehicle control groups received the vehicle(0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid [4:1, v/v]). The study for the rats was designed to continue for up to 104 weeks and all surviving male rats were sacrificed during Week 105.

The survival analyses did not show a statistically significant dose response relationship in mortality across the combined vehicle control group and treated groups for either males or females. The pairwise comparisons did not show statistically significant differences in mortality between the combined vehicle control group and each of the treated groups for either males or females, except the differences between the combined vehicle control group and the 10 mg/kg/day group in females. However, the difference between the combined vehicle control group and the 10mg/kg/day group is a negative finding.

The tumor analysis did not show any tumor types had a statistically significant positive dose response in either males or females. The pairwise comparisons did not show any statistically significant increases in incidence in any observed tumor types in any treated groups in either males or females.

Mouse Study: One hundred CB6F1-Tg rasH2 mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There are 15 mice of each sex in the positive control group. The dose levels for treated groups were 50, 150, and 500 mg/kg/day. The mice in the vehicle control group received the vehicle (0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid (4:1, v/v)). The study was designed to continue for up to 26 weeks for both sexes and all surviving mice were sacrificed during Week 27. The mice in the positive control group received a single intraperitoneal injection of N-nitroso-N-methylurea (MNU) at 75 mg/kg on Day 1. Positive control animals were sacrificed on Day 134 (males) or Day 154 (females).

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control and treated groups for either males or females.

The pairwise comparisons showed a statistically significant increase in mortality in the positive control group for both the male and female mice.

The trend test showed statistically significant positive dose response relationship in incidence of hemangiosarcoma in spleen (p-value=0.0129<0.05) and combined tumors of hemangiosarcoma and hemangioma in the whole body (p-value=0.0205<0.05) between the vehicle control and the treated groups in male mice

The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of malignant lymphoma in hematophoietic (p-value<0.001), forestomach papilloma in stomach (p-value<0.001) and squamous cell carcinoma in stomach (p-value=0.0017<0.05) in male mice; malignant lymphoma in hematophoietic (p-value<0.001), papilloma in skin (p-value<0.001) and forestomach papilloma in stomach (p-value<0.001) in female mice.

Zhuang Miao, Ph.D.
Mathematical Statistician

Concur:
Feng Zhou, MS
Mathematical Statistician, Biometrics-6

Karl Lin, Ph.D.
Mathematical Statistician, Team Leader, Biometrics-6

cc:
Archival NDA 212028
Yi Tsong, Ph.D.
Avila, Amy, Ph.D.

6. Appendix

Table 7: Intercurrent Mortality Rate -Male Rats

	Combined Vehicle 0 mg|kg|day (N=-120)		30 mg|kg|day (N=-60)		100 mg|kg|day (N=-60)		300 mg|kg|day (N=-60)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	2.50	1	1.67	.	.	2	3.33
53 - 78	4	5.83	1	3.33	7	11.67	5	11.67
79 - 91	8	12.50	7	15.00	5	20.00	4	18.33
92 - 105	18	25.83	4	20.00	8	33.33	6	28.33
Ter. Sac.	87	72.50	47	78.33	40	66.67	43	71.67

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Rate -Female Rats

	Combined Vehicle 0 mg|kg|day (N=-120)		10 mg|kg|day (N=-60)		30 mg|kg|day (N=-60)		100 mg|kg|day (N=-60)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	2.50	.	.	.	.	1	1.67
53 - 78	2	4.17	1	1.67	2	3.33	1	3.33
79 - 91	7	10.00	1	3.33	4	10.00	6	13.33
92 - 105	20	26.67	5	11.67	3	15.00	1	15.00
Ter. Sac.	88	73.33	53	88.33	51	85.00	51	85.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Combined Vehicle vs. Low	P_Value Combined Vehicle vs. Medium	P_Value Combined Vehicle vs. High
Dose-Response	Likelihood Ratio	0.5903	0.7997	0.3583	0.4247
Homogeneity	Log-Rank	0.5202	0.7983	0.3491	0.4298

Table 10: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Combined Vehicle vs. Low	P_Value Combined Vehicle vs. Medium	P_Value Combined Vehicle vs. High
Dose-Response	Likelihood Ratio	0.1962	0.0155	0.0902	0.1008
Homogeneity	Log-Rank	0.0586	0.0215	0.1014	0.1126

Table 11: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	30 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	100 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	300 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
ABDOMINAL CAVITY	LIPOSARCOMA	0/120 (109) 0.5933	1/60 (55) 0.3354	0/60 (52) NC	0/60 (52) NC
ADRENALS	CORTICAL ADENOMA	1/120 (109) 0.3814	1/60 (55) 0.5596	0/60 (52) 1.0000	1/60 (52) 0.5430
	CORTICAL CARCINOMA	0/120 (109) 0.1940	0/60 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
	MALIGNANT PHEOCHROMOCYTOMA	1/120 (109) 0.3260	1/60 (55) 0.5596	1/60 (52) 0.5430	1/60 (52) 0.5430
	PHEOCHROMOCYTOMA	12/120 (109) 0.9531	7/60 (55) 0.4649	5/60 (52) 0.6993	2/60 (52) 0.9727
Adrenals	C_Cortical Adenoma+Carc	1/120 (109) 0.1334	1/60 (55) 0.5596	0/60 (52) 1.0000	2/60 (52) 0.2441
	C_Pheochromocytoma	13/120 (109) 0.9152	8/60 (55) 0.4031	6/60 (52) 0.6215	3/60 (52) 0.9398
BRAIN	ASTROCYTOMA	2/120 (109) 0.2271	1/60 (56) 0.7144	1/60 (52) 0.6925	2/60 (53) 0.3963
	GRANULAR CELL TUMOR	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
	OLIGODENDROGLIOMA	0/120 (109) 0.1970	0/60 (55) NC	0/60 (52) NC	1/60 (53) 0.3272
COAGULATING GLANDS	ADENOCARCINOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/59 (51) 1.0000
EARS	SQUAMOUS CELL PAPILLOMA	1/120 (109) 0.3510	0/60 (55) 1.0000	0/60 (52) 1.0000	1/60 (52) 0.5430
HARDERIAN GLANDS	ADENOCARCINOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/59 (51) 1.0000
HEART	SCHWANNOMA, ENDOCARDIAL	1/120 (109) 0.3510	0/60 (55) 1.0000	0/60 (52) 1.0000	1/60 (52) 0.5430
HEMATOPOIETIC AND	HISTIOCYTIC SARCOMA	1/120 (109) 0.0415	1/60 (56) 0.5650	0/60 (52) 1.0000	3/60 (53) 0.1030
	MALIGNANT LYMPHOMA	4/120 (110) 0.6515	1/60 (56) 0.8762	2/60 (52) 0.6279	1/60 (52) 0.8599
ILEUM	ADENOCARCINOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
LIVER	CHOLANGIOMA	0/120 (109) 0.1940	0/60 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
	HEPATOCELLULAR ADENOMA	2/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	30 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	100 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	300 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
LUNG	ADENOMA, BRONCHIOLO-ALVEOLAR	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
	SQUAMOUS CELL CARCINOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
MAMMARY GLAND	ADENOCARCINOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
	FIBROADENOMA	0/120 (109) 0.5933	1/60 (55) 0.3354	0/60 (52) NC	0/60 (52) NC
MESENTERIC LYMPH N	HEMANGIOSARCOMA	0/120 (109) 0.1940	0/59 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
OTHER BONE	OSTEOSARCOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
PANCREAS	ISLET-CELL ADENOMA	8/120 (109) 0.2846	0/60 (55) 1.0000	1/60 (52) 0.9733	4/60 (52) 0.5822
PARATHYROIDS	ADENOMA	1/116 (105) 1.0000	0/56 (51) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
PITUITARY	ADENOCARCINOMA, PARS DISTALIS	7/120 (110) 0.5431	4/60 (56) 0.5422	6/60 (52) 0.2028	3/60 (53) 0.6885
	ADENOMA, PARS DISTALIS	25/120 (111) 0.3140	14/60 (56) 0.4307	13/60 (54) 0.4851	14/60 (53) 0.3588
	ADENOMA, PARS INTERMEDIA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
PROSTATE	ADENOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
SKELETAL MUSCLE	RHABDOMYOSARCOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
SKIN	BASAL CELL CARCINOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
	BASAL CELL TUMOR	0/120 (109) 0.1940	0/60 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
	KERATOACANTHOMA	6/120 (109) 0.5465	0/60 (55) 1.0000	1/60 (52) 0.9389	2/60 (52) 0.7944
	SQUAMOUS CELL CARCINOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
	SQUAMOUS CELL PAPILLOMA	0/120 (109) 0.1659	1/60 (55) 0.3354	1/60 (52) 0.3230	1/60 (52) 0.3230
Skin	C_Keratoa+squamous cell Papill+Carci	6/120 (109) 0 3509	1/60 (55) 0 9464	3/60 (52) 0 6017	3/60 (52) 0 6017
SPLEEN	HEMANGIOSARCOMA	1/120 (109) 0.3510	0/60 (55) 1.0000	0/60 (52) 1.0000	1/60 (52) 0.5430

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	30 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	100 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	300 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
STOMACH	LEIOMYOSARCOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
	SQUAMOUS CELL PAPILLOMA	0/120 (109) 0.5933	1/60 (55) 0.3354	0/60 (52) NC	0/60 (52) NC
SUBCUTIS	FIBROMA	5/120 (109) 0.4056	0/60 (55) 1.0000	3/60 (52) 0.5082	2/60 (52) 0.7228
	FIBROSARCOMA	0/120 (109) 0.3881	0/60 (55) NC	2/60 (53) 0.1057	0/60 (52) NC
	LIPOMA	0/120 (109) 0.5933	1/60 (55) 0.3354	0/60 (52) NC	0/60 (52) NC
TAIL	FIBROMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
	FIBROSARCOMA	0/120 (109) 0.1940	0/60 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
	SQUAMOUS CELL PAPILLOMA	0/120 (109) 0.3881	0/60 (55) NC	1/60 (52) 0.3230	0/60 (52) NC
TESTES	HEMANGIOMA	1/120 (109) 1.0000	0/60 (55) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000
	INTERSTITIAL CELL ADENOMA	2/120 (109) 0.4848	0/60 (55) 1.0000	0/60 (52) 1.0000	1/60 (52) 0.6925
	MALIGNANT SEMINOMA	0/120 (109) 0.1940	0/60 (55) NC	0/60 (52) NC	1/60 (52) 0.3230
THYMUS	MALIGNANT THYMOMA	1/116 (106) 1.0000	0/58 (54) 1.0000	0/59 (51) 1.0000	0/55 (48) 1.0000
THYROIDS	C-CELL ADENOMA	10/120 (109) 0.9102	0/59 (54) 1.0000	4/60 (52) 0.7221	1/60 (52) 0.9885
	FOLLICULAR CELL ADENOMA	0/120 (109) 0.1135	0/59 (54) NC	1/60 (52) 0.3230	1/60 (52) 0.3230
TRIGEMINAL GANGLIO	MALIGNANT SCHWANNOMA	0/120 (109) 0.1970	0/60 (55) NC	0/60 (52) NC	1/60 (53) 0.3272
Whold Body	C_hemangiosar+heman	2/120 (109) 0.1760	0/60 (55) 1.0000	0/60 (52) 1.0000	2/60 (52) 0.3888

Table 12: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	10 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	30 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	100 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
ABDOMINAL CAVITY	MALIGNANT MESOTHELIOMA	0/120 (109) 0.6079	1/60 (58) 0.3473	0/60 (56) NC	0/60 (55) NC
ADRENALS	CORTICAL ADENOMA	1/120 (109) 0.3571	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (55) 0.5596
	MALIGNANT PHEOCHROMOCYTOMA	3/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
	PHEOCHROMOCYTOMA	2/120 (109) 0.4956	1/60 (58) 0.7246	1/60 (56) 0.7144	1/60 (55) 0.7091
Adrenals	C_Pheochromocytoma	5/120 (109) 0.8005	1/60 (58) 0.9264	1/60 (56) 0.9208	1/60 (55) 0.9178
BRAIN	ASTROCYTOMA	0/120 (109) 0.3993	0/60 (58) NC	1/60 (56) 0.3394	0/60 (55) NC
	MALIGNANT MENINGIOMA	0/120 (109) 0.6093	1/60 (59) 0.3512	0/60 (56) NC	0/60 (55) NC
EYES	MALIGNANT MELANOMA	0/120 (109) 0.3993	0/60 (58) NC	1/60 (56) 0.3394	0/60 (55) NC
HEART	SCHWANNOMA, ENDOCARDIAL	0/120 (109) 0.2014	1/60 (58) 0.3473	0/60 (56) NC	1/60 (55) 0.3354
HEMATOPOIETIC AND	HISTIOCYTIC SARCOMA	3/120 (110) 0.2758	0/60 (58) 1.0000	0/60 (56) 1.0000	2/60 (57) 0.5569
	MALIGNANT LYMPHOMA	4/120 (110) 0.6961	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (56) 0.8762
LIVER	HEPATOCELLULAR ADENOMA	2/120 (109) 0.4908	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (56) 0.7144
	HEPATOCELLULAR CARCINOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
Liver	C_Hepatocellular Aden+carc	3/120 (109) 0.6021	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (56) 0.8131
MAMMARY GLAND	ADENOCARCINOMA	15/120 (113) 0.9418	6/60 (59) 0.7963	6/60 (56) 0.7613	3/60 (56) 0.9729
	ADENOMA	7/120 (110) 0.9931	1/60 (58) 0.9692	1/60 (56) 0.9660	0/60 (55) 1.0000
	FIBROADENOMA	25/120 (110) 0.9992	6/60 (58) 0.9879	9/60 (57) 0.8975	2/60 (55) 0.9999
OVARIES	LUTEOMA	0/120 (109) 0.1978	0/60 (58) NC	0/60 (56) NC	1/60 (55) 0.3354
PANCREAS	ISLET-CELL ADENOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	10 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	30 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	100 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
PITUITARY	ADENOCARCINOMA, PARS DISTALIS	23/119 (110) 0.9907	8/60 (58) 0.9121	5/60 (56) 0.9881	4/60 (55) 0.9953
	ADENOMA, PARS DISTALIS	41/119 (111) 0.9997	18/60 (59) 0.8431	20/60 (57) 0.6557	7/60 (57) 0.9999
	ADENOMA, PARS INTERMEDIA	1/119 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
RECTUM	ADENOMA	0/120 (109) 0.3993	0/60 (58) NC	1/60 (56) 0.3394	0/60 (55) NC
SKIN	BASAL CELL CARCINOMA	0/120 (109) 0.6079	1/60 (58) 0.3473	0/60 (56) NC	0/60 (55) NC
	KERATOACANTHOMA	1/120 (109) 0.8471	1/60 (58) 0.5754	0/60 (56) 1.0000	0/60 (55) 1.0000
	SQUAMOUS CELL CARCINOMA	0/120 (109) 0.3993	0/60 (58) NC	1/60 (56) 0.3394	0/60 (55) NC
	SQUAMOUS CELL PAPILLOMA	1/120 (109) 0.3571	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (55) 0.5596
Skin	C_Keratoa+squamous cell Papill+Carci	2/120 (109) 0.4956	1/60 (58) 0.7246	1/60 (56) 0.7144	1/60 (55) 0.7091
SPINAL CORD	ASTROCYTOMA	1/120 (110) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
STOMACH	LIPOMA	0/120 (109) 0.1978	0/60 (58) NC	0/60 (56) NC	1/60 (55) 0.3354
SUBCUTIS	FIBROMA	2/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
	LEIOMYOMA	0/120 (109) 0.6079	1/60 (58) 0.3473	0/60 (56) NC	0/60 (55) NC
	LIPOMA	1/120 (109) 0.8471	1/60 (58) 0.5754	0/60 (56) 1.0000	0/60 (55) 1.0000
	LIPOSARCOMA	0/120 (109) 0.2007	0/60 (58) NC	0/60 (56) NC	1/60 (56) 0.3394
	RHABDOMYOSARCOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
Subcutis	C_Liposarcoma+Rhabdomy	1/120 (109) 0.3617	0/60 (58) 1.0000	0/60 (56) 1.0000	1/60 (56) 0.5650
THYMUS	SQUAMOUS CELL CARCINOMA	0/115 (106) 0.4036	0/60 (58) NC	1/59 (56) 0.3457	0/60 (55) NC
	THYMOMA	0/115 (106) 0 2036	0/60 (58) NC	0/59 (55) NC	1/60 (56) 0 3457
THYROIDS	C-CELL ADENOMA	5/120 (110) 0.3014	1/60 (58) 0.9249	3/60 (56) 0.5444	3/60 (55) 0.5343

Organ Name	Tumor Name	0 mg/kg/day Combined Vehicle (N=120) P-value - Trend	10 mg/kg/day Low (N=60) P-value – Combined Vehicle vs. Low	30 mg/kg/day Med (N=60) P-value – Combined Vehicle vs. Med	100 mg/kg/day High (N=60) P-value – Combined Vehicle vs. High
	C-CELL CARCINOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
	FOLLICULAR CELL ADENOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
Thyroids	C_C cell Aden+Carc	6/120 (110) 0.3826	1/60 (58) 0.9518	3/60 (56) 0.6379	3/60 (55) 0.6280
URINARY BLADDER	PAPILLOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
UTERUS	ENDOMETRIAL ADENOCARCINOMA	2/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
	ENDOMETRIAL STROMAL POLYP	8/120 (109) 0.4082	2/60 (58) 0.9179	1/60 (56) 0.9787	4/60 (55) 0.6190
	ENDOMETRIAL STROMAL SARCOMA	1/120 (109) 0.5657	0/60 (58) 1.0000	2/60 (56) 0.2660	0/60 (55) 1.0000
	GRANULAR CELL TUMOR	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
	LEIOMYOMA	1/120 (109) 1.0000	0/60 (58) 1.0000	0/60 (56) 1.0000	0/60 (55) 1.0000
Uterus	C_Endometrial stromal polyp+sarcoma	9/120 (109) 0.4769	2/60 (58) 0.9433	3/60 (56) 0.8400	4/60 (55) 0.6921
VAGINA	SQUAMOUS CELL CARCINOMA	0/120 (109) 0.3993	0/60 (58) NC	1/60 (56) 0.3394	0/60 (55) NC
	STROMAL SARCOMA	0/120 (109) 0.2007	0/60 (58) NC	0/60 (56) NC	1/60 (56) 0.3394
	VAGINAL POLYP	1/120 (109) 0.8444	2/60 (58) 0.2768	0/60 (56) 1.0000	0/60 (55) 1.0000

Table 13: Intercurrent Mortality Rate -Male Mice

	Vehicle 0 mg|kg|day (N=25)		Low 50 mg|kg|day (N=25)		Middle 150 mg|kg|day (N=25)		High 500 mg|kg|day (N=25)		Positive MNU: 75 (N=15)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	1	4.00	2	13.33
14 - 26	1	4.00	.	.	.	.	1	8.00	5	33.33
Ter. Sac.	24	96.00	25	100.00	25	100.00	23	92.00	8(week 19)	53.33

Cum. %: Cumulative percentage except for Ter. Sac.

Table 14: Intercurrent Mortality Rate -Female Mice

	Vehicle 0 mg|kg|day (N=25)		Low 50 mg|kg|day (N=25)		Middle 150 mg|kg|day (N=25)		High 500 mg|kg|day (N=25)		Positive MNU: 75 (N=15)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	1	6.67
14 - 26	.	.	2	8.00	2	8.00	.	.	5	33.33
Ter. Sac.	25	100.00	23	92.00	23	92.00	25	100.00	9(week 22)	60.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 15: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control -Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.1781	0.2390	0.2390	0.5362	<0.0001
Homogeneity	Log-Rank	0.2814	0.3173	0.3173	0.5396	<0.0001

Table 16: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control --Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.4021	0.0935	0.0935	.	<0.0001
Homogeneity	Log-Rank	0.2483	0.1531	0.1531	.	<0.0001

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	150 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	500 mg/kg/day High (N=25) P-value - Vehicle vs. High
ILEUM	HEMANGIOMA	0/25 (25) 0.7449	1/25 (25) 0.5000	0/25 (25) NC	0/25 (23) NC
LUNG	ADENOMA, BRONCHIOLO-ALVEOLAR	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000
	CARCINOMA, BRONCHIOLO-ALVEOLAR	1/25 (25) 0.9369	1/25 (25) 0.7551	0/25 (25) 1.0000	0/25 (23) 1.0000
Lung	C_alveolar bronchiolar Adeno+Carcin	2/25 (25) 0.9849	1/25 (25) 0.8827	0/25 (25) 1.0000	0/25 (23) 1.0000
SKIN	PAPILLOMA	0/25 (25) 0.7449	1/25 (25) 0.5000	0/25 (25) NC	0/25 (23) NC
SPLEEN	HEMANGIOSARCOMA	0/25 (25) 0.0129	0/25 (25) NC	0/25 (25) NC	3/25 (24) 0.1099
STOMACH	PAPILLOMA, FORESTOMACH	0/25 (25) 0.2347	0/25 (25) NC	0/25 (25) NC	1/25 (23) 0.4792
SUBMAXILLARY LYMPH	HEMANGIOMA	0/25 (25) 0.7449	1/25 (25) 0.5000	0/25 (25) NC	0/25 (23) NC
TESTES	HEMANGIOSARCOMA	0/25 (25) 0.2347	0/25 (25) NC	0/25 (25) NC	1/25 (23) 0.4792
Whole Body	C_Hemangiosarcoma+hemangioma	0/25 (25) 0.0205	2/25 (25) 0.2449	0/25 (25) NC	4/25 (24) 0.0502

Table 18: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
HEMATOPOIETIC AND	MALIGNANT LYMPHOMA	0/25 (25)	10/15 (11) <0.001
ILEUM	HEMANGIOMA	0/25 (25)	0/15 (5) NC
LUNG	ADENOMA, BRONCHIOLO-ALVEOLAR	1/25 (25)	0/15 (5) 1.0000
	CARCINOMA, BRONCHIOLO-ALVEOLAR	1/25 (25)	0/15 (5) 1.0000
Lung	C_alveolar bronchiolar Adeno+Carcin	2/25 (25)	0/15 (5) 1.0000
SKIN	PAPILLOMA	0/25 (25)	0/15 (5) NC
STOMACH	PAPILLOMA, FORESTOMACH	0/25 (25)	11/15 (12) <0.001
	SQUAMOUS CELL CARCINOMA	0/25 (25)	4/15 (8) 0.0017
SUBMAXILLARY LYMPH	HEMANGIOMA	0/25 (25)	0/14 (5) NC
TESTES	HEMANGIOSARCOMA	0/25 (25)	1/15 (6) 0.1935
Whole Body	C_Hemangiosarcoma+hemangioma	0/25 (25)	1/15 (6) 0.1935

Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	150 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	500 mg/kg/day High (N=25) P-value - Vehicle vs. High
ADIPOSE TISSUE	HEMANGIOMA	0/25 (25) 0.4949	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC
HEMATOPOIETIC AND	MALIGNANT LYMPHOMA	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000
SPLEEN	HEMANGIOSARCOMA	1/25 (25) 0.2399	1/25 (25) 0.7551	0/25 (24) 1.0000	2/25 (25) 0.5000
SUBCUTIS	HEMANGIOSARCOMA	0/25 (25) 0.5000	0/25 (25) NC	1/25 (25) 0.5000	0/25 (25) NC
THYMUS	THYMOMA	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000
VERTEBRA	HEMANGIOSARCOMA	0/25 (25) 0.4949	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (25) 0.2908	1/25 (25) 0.7551	3/25 (25) 0.3046	2/25 (25) 0.5000

Table 20: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
ADIPOSE TISSUE	HEMANGIOMA	0/25 (25)	0/15 (8) NC
HEMATOPOIETIC AND	MALIGNANT LYMPHOMA	0/25 (25)	9/15 (12) <0.001
ILEUM	ADENOCARCINOMA	0/25 (25)	1/15 (8) 0.2424
SKIN	PAPILLOMA	0/25 (25)	6/15 (10) <0.001
SPLEEN	HEMANGIOSARCOMA	1/25 (25)	0/15 (8) 1.0000
STOMACH	PAPILLOMA, FORESTOMACH	0/25 (25)	14/15 (14) <0.001
	SQUAMOUS CELL CARCINOMA	0/25 (25)	1/15 (8) 0.2424
SUBCUTIS	HEMANGIOSARCOMA	0/25 (25)	0/15 (8) NC
	SQUAMOUS CELL CARCINOMA	0/25 (25)	1/15 (8) 0.2424
THYMUS	THYMOMA	1/25 (25)	0/15 (8) 1.0000
TONGUE	SQUAMOUS CELL PAPILLOMA	0/25 (25)	1/15 (8) 0.2424
VERTEBRA	HEMANGIOSARCOMA	0/25 (25)	0/15 (8) NC
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (25)	0/15 (8) 1.0000

Figure 1: Kaplan-Meier Survival Functions for Male Rats

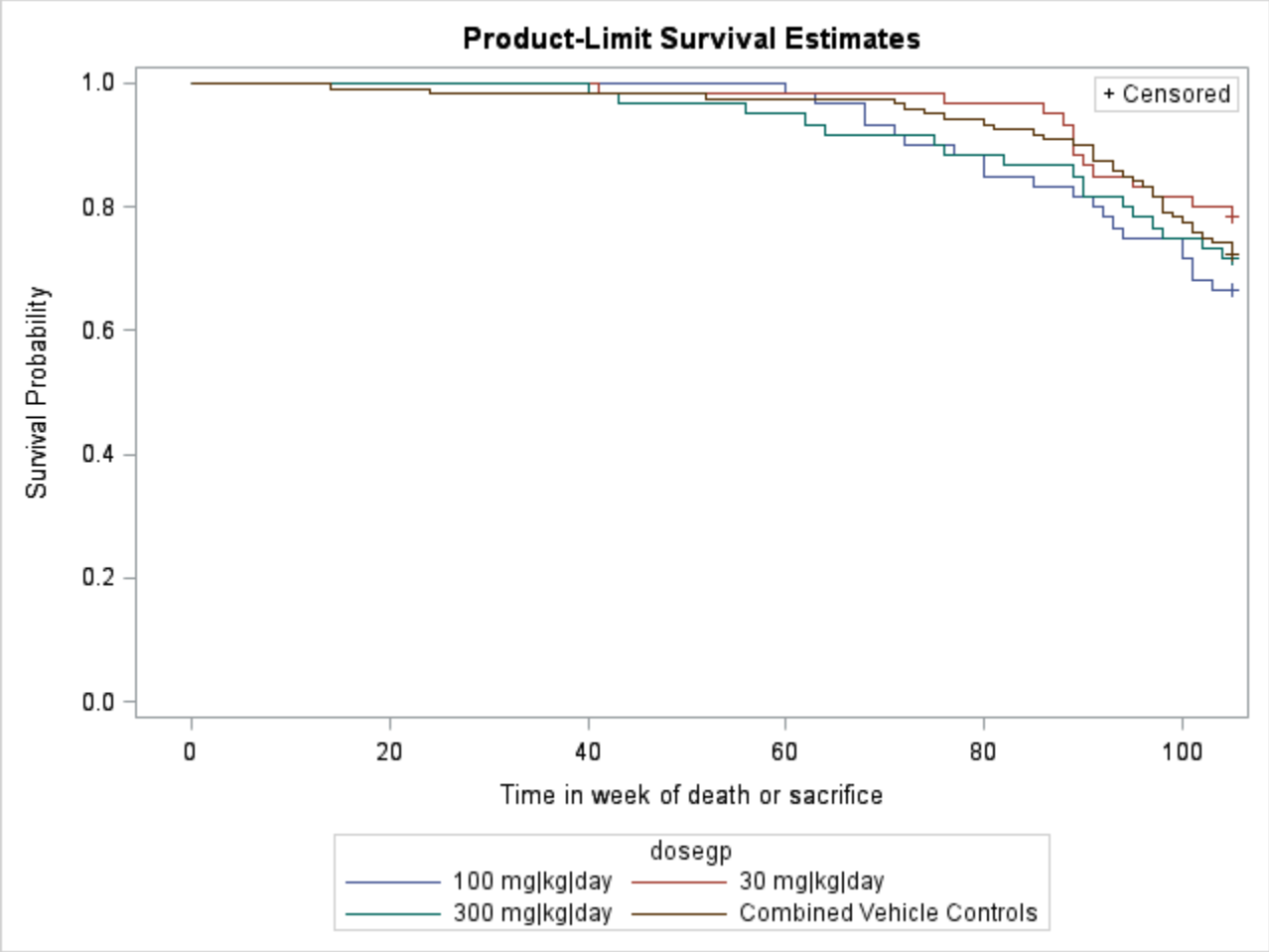

Figure 2: Kaplan-Meier Survival Functions for Female Rats

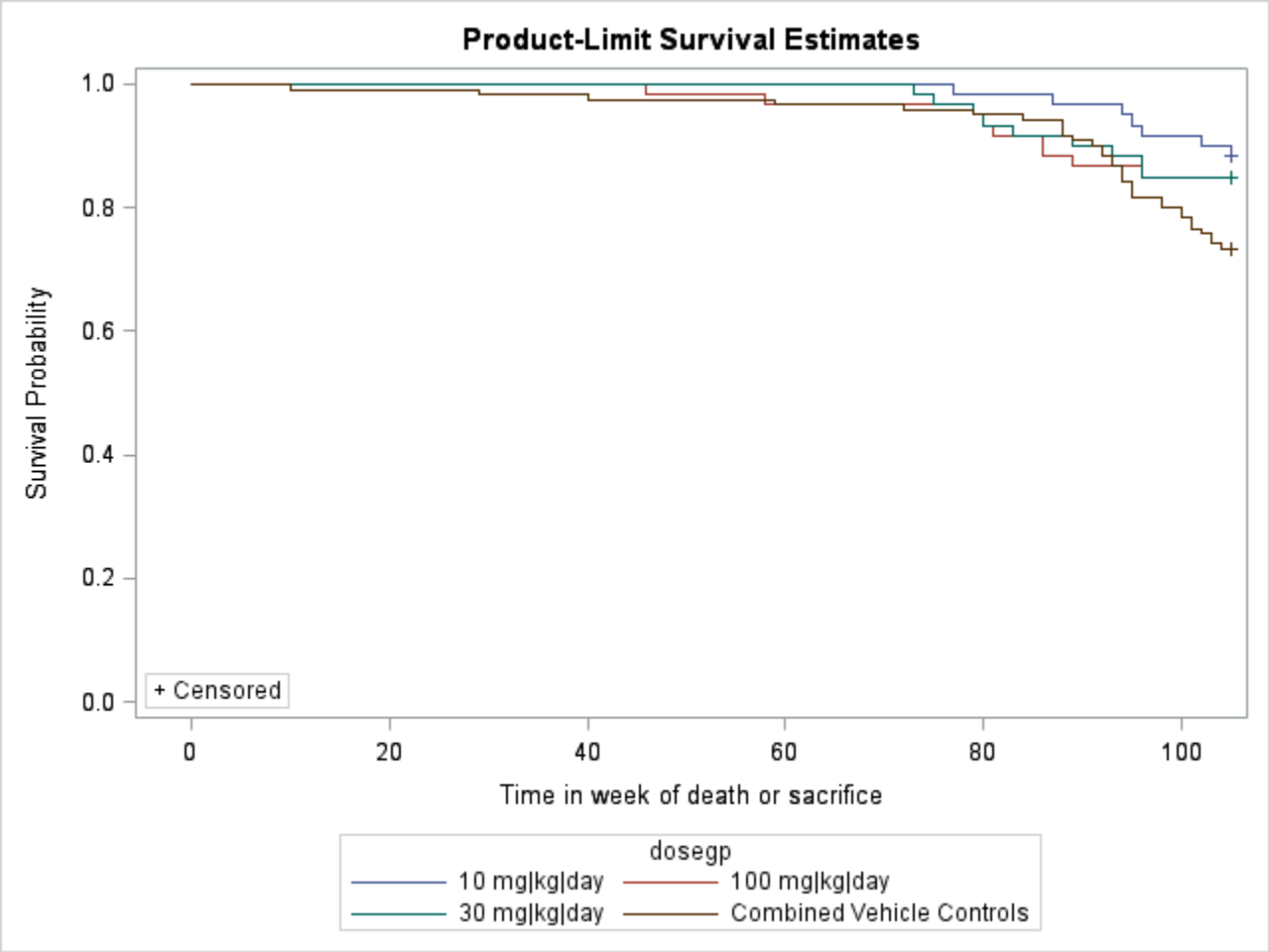

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Figure 3: Kaplan-Meier Survival Functions for Male Mice

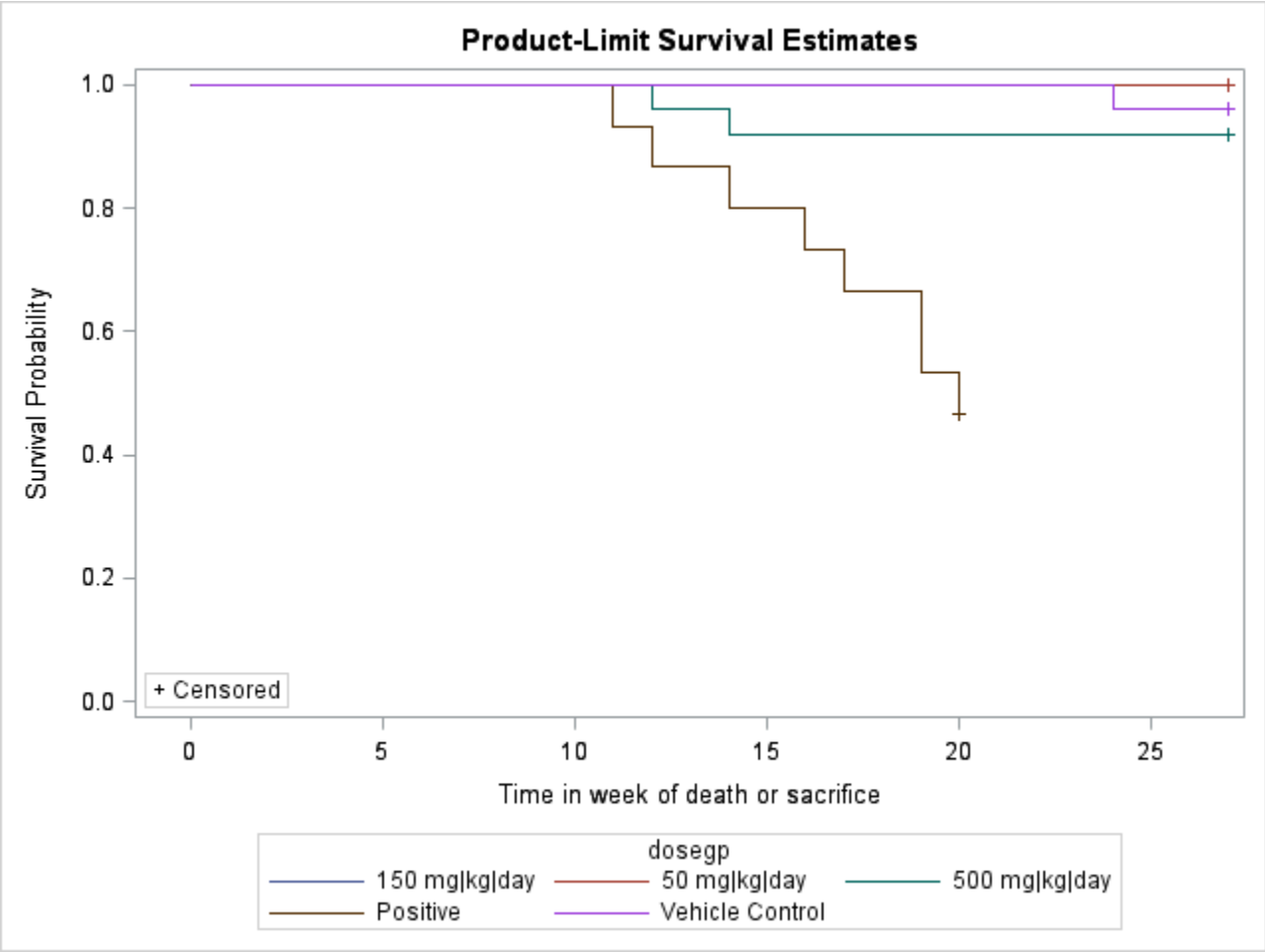
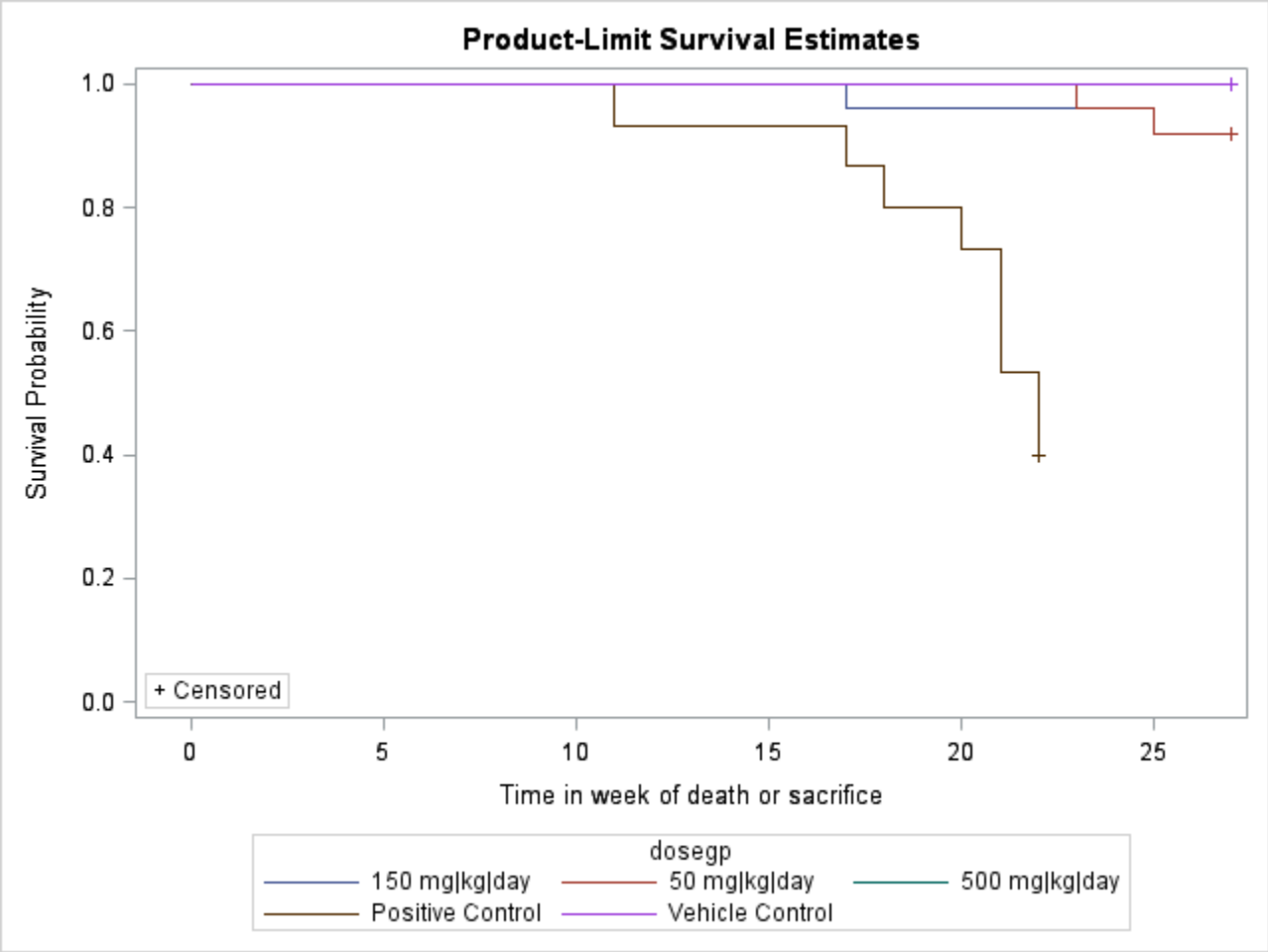


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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Concur with review.

YI TSONG
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